SUBSTITUTION, ELIMINATION, ADDITION, AND REARRANGEMENT REACTIONS PROMOTED BY POTASSIUM SALTS SOLUBILIZED BY 18-CROWN-6 ("NAKED" ANIONS) IN NON-POLAR AND DIPOLAR APROTIC ORGANIC SOLVENTS

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Date approved by Chairman: NOV 22 1976

To my parents

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF ILLUSTRATIONS

Figure | Page

SUMMARY

The work described in this thesis involved studies of the effects of 18-crown-6 on the solubility and reactivity of potassium salts in non-polar and dipolar aprotic organic solvents.

The solubilities of a variety of common potassium salts in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 were measured using a Coleman Model-21 Flame Photometer. The order of solubilities of potassium salts in 0.15M 18-crown-6-acetonitrile solution at 25°C was found to be KSCN > KI > KN_3 ≈ KBr ≈ KCN > KOAc ≫ KCl ≫ KF. The solubility enhancement caused by the presence of 18-crown-6, is quite dramatic for KCl, KCN, and KOAc (greater than 10^2), only moderate for KBr and KN_3 (greater than 50), and marginal for KF, KI, and KSCN. It should be noted that KI and KSCN already have high inherent solubilities in pure acetonitrile.

It has been found that the solubilization of alkali metal salts in polar and non-polar aprotic organic solvents by 18-crown-6 leaves the companion anions weakly solvated. These are referred to as "naked" anions. These species have been found effective in promoting dehydrohalogenation of 2-chloro-2-methylcyclohexanone, a substrate subject to "Favorskii rearrangements", in the non-polar and dipolar aprotic

organic solvents benzene and acetonitrile. Among the "naked" halides, bromide has been found to be the most effective. The investigation of the use of "naked" cyanide in promoting dehydrohalogenation and/or substitution of 2-chloro-2-methylcyclohexanone resulted in a new and facile substitution at an α-tertiary carbon center. At room temperature a quantitative conversion to the simple displacement product, 2-cyano-2-methylcyclohexanone, was obtained thus providing a potentially useful procedure for introducing a carbon functionality at a rather sterically hindered position. The reaction proceeded at a faster rate in acetonitrile than in benzene. Excellent yields of products were obtained in the absence of the crown ether in acetonitrile but reaction times were quite long. At reflux temperature the "Favorskii rearrangement product", 1-methylcyclopentanecarbonylcyanide, was obtained in high yield. The latter product was also obtained simply by heating 2-cyano-2-methylcyclohexanone with the "naked" cyanide reagent.

Reaction of "naked" cyanide with cis-2-chloro-4-methylcyclohexanone, a substrate subject to "Favorskii rearrangements", proceeded smoothly at room temperature to the displacement product, cis-2-cyano-4-methylcyclohexanone, in good yields. Reaction of "naked" acetate with the same substrate occurred only very slowly at room temperature. At reflux temperature, however, the reaction was smoothly effected to the simple displacement product, cis-2-acetoxy-4-

methylcyclohexanone. It is interesting to note that no "Favorskii rearrangement product" was obtained in the latter case even though the reaction was refluxed for seven hours. Moreover, little or no reaction was found to take place in the absence of 18-crown-6 under the same conditions covering the same periods of time.

It has been demonstrated that "naked" cyanide in conjunction with acetone cyanohydrin provides a simple and stereoselective hydrocyanation reagent using Δ^4-cholesten-3-one as the substrate. No reaction was observed in the absence of 18-crown-6, acetone cyanohydrin, or potassium cyanide. In the presence of acetone cyanohydrin, however, the reaction proceeded smoothly and excellent yields of hydrocyanation products were obtained in benzene and acetonitrile. No cyanide hydrolysis products or dimers could be detected. Moreover, the lower the temperature the greater the preference for formation of the more thermodynamically stable product, the cis-isomer. At ambient temperature a cis/trans ratio of 10/1 was obtained in benzene compared to a cis/trans ratio of 3.9/1 obtained in acetonitrile. The Michael addition of "naked" cyanide to cholestenone was the first stereoselective application of the procedure and the stereochemical results and product yields appeared to be equal to or superior to other hydrocyanating reagents.

The reactions of "naked" anions so far reported were carried out under solid-liquid phase-transfer catalytic

(heterogeneous) conditions with the 18-crown-6 acting as the phase-transfer catalyst. The reactions of "naked" anions with organic substrates in liquid-liquid phase-transfer catalytic conditions have also been investigated. The reactions of "naked" cyanide and of "naked" acetate with primary and secondary octyl halides have been investigated. The reactions described in this thesis were carried out in the presence and in the absence of 18-crown-6 using aqueous KCN or KOAc. The following conclusions could be drawn from the data: (i) at 1^{o} and 2^{o} positions, the bromides were displaced more rapidly than the chlorides in all cases; (ii) with 1^{o} substrates, no elimination products were found, and the yields were essentially quantitative; (iii) with secondary substrates, a small percentage of alkenes and a high yield of substitution products were obtained, the conversions being essentitally quantitative; (iv) in all cases, crown was present in catalytic quantities, indicating that it behaved as a phase-transfer catalyst; (v) little or no reaction was found to take place in the absence of 18-crown-6 under the same conditions covering the same periods of time; and (vi) reaction times were relatively short, and the product yields were comparable to yields obtained by other synthetic methods.

CHAPTER I

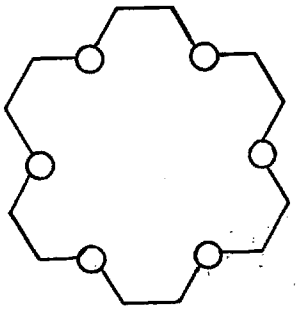
INTRODUCTION, CROWN ETHERS

"Naked" Anions

Crown ethers were discovered in 1967 by Pedersen[1-11] who showed them to be strong complexing agents for metal cations. Alkali metal salts were found to be easily solubilized in polar and non-polar aprotic solvents producing a solution of a complexed metal cation and a weakly solvated anion. These anionic species have been referred to as "naked" anions.[12] This discovery has proved of great synthetic importance and has paved the way toward the development of useful and new synthetic reagents.[13]

In the reactions of metal salts with hydrophobic organic substrates the limited solubility of metal salts in organic solvents requires two-phase reaction conditions. It has been found, however, that these reactions are greatly facilitated by the use of catalytic amounts of crown ethers as phase-transfer catalysts between solid and liquid phases. Crown ethers can catalyze these reactions by solubilizing the salts and by increasing the dissociation of ion pairs to provide highly reactive "naked" anions. Of all the crown ethers, 18-crown-6, 1, is the simplest and most synthetically useful at this juncture. Other very important crown ethers

are dicyclohexyl-18-crown-6 and dibenzyl-18-crown-6, 2 and 3, respectively.[4,10,14-19]



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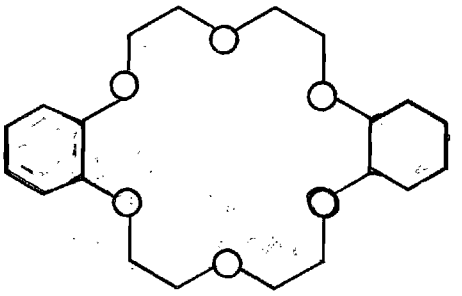

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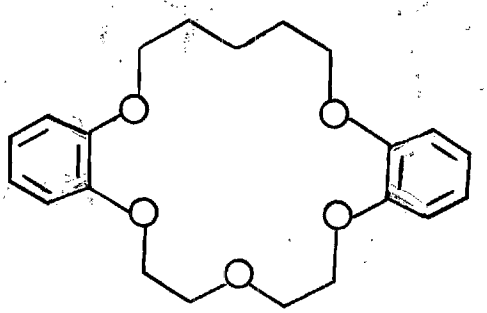


3

New and improved syntheses of various crown ether systems,[17-23] including 18-crown-6, 15-crown-5, and 12-crown-4 have recently been reported.[17-26] Crown ethers containing nitrogen and sulfur heteroatoms have also been synthesized.[7, 13g, 18, 21-23, 27] Crown ether derivatives have also been reported in polymeric forms with molecular weights up to 100,000.[28-31] A large number of crown ether complexes of various salts have also been reported.[27, 32-37]

Nomenclature[13g]

Pedersen first gave macrocyclic polyethers the trivial nomenclature of "crown" compounds. The trivial names were assigned on the following basis: (i) the number and kind of hydrocarbon rings, if present; (ii) the total number of atoms in the polyether ring; (iii) the class name, crown; and (iv) the number of oxygen atoms in the polyether ring. For example, structure 1 has the systematic name, 1, 4, 7, 10, 13, 16-hexaoxacyclooctadecane or 18-crown-6 by the trivial nomenclature. Similarly, structure 2 has the systematic name 2, 5, 8, 15, 21-hexaoxatricyclo [20.4.0.0]-hexacosane[17-18] or dicyclohexyl-18-crown-6 by the trivial nomenclature.

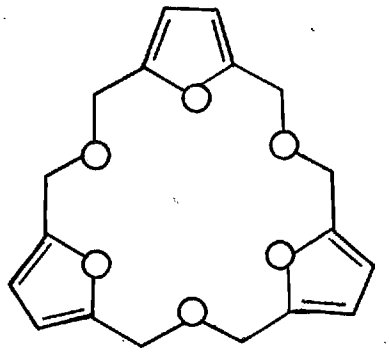
Biological Utilization of Crown Ethers

Considerable attention has been given to this family of compounds as model carriers in biological ion transport systems,[38-43] and, unlike neutral macrocyclic antibiotics which influence transport of metal cations across cell membranes *via* complexation,[44] the crowns were reported efficient in membrane transport studies[45] (crowns have served as carrier models for very complex antibiotics such as nonactin).[46] Crown ethers have also been reported as effective additives in the formation of glucosides.[46] In addition, ion-selective electrodes produced by various crown complexations as well

as extraction techniques for cesium and carboxylic acids have also been reported.[47]

Chiral crowns synthesized by Cram and coworkers[48-52] were utilized to separate enantiomers of ammonium salts and to selectively complex enantiomers of amino acids in solution. Dibenzo-18-crown-6 has been shown to form 1:1 adducts with phenoxymethyl penicillin and with salicylic acid in chloroform.[53]

In a number of interesting publications, Cram reported[54-61] the first synthesis of a series of substituted and/or unsubstituted 18-crown-6 compounds. These compounds were themselves hosts for binding organic and inorganic cations. An 18-crown-6 compound 4 containing furanyl units spaced in many possible ways as part of the multiheteromacrocycles was also reported by Cram.[58]



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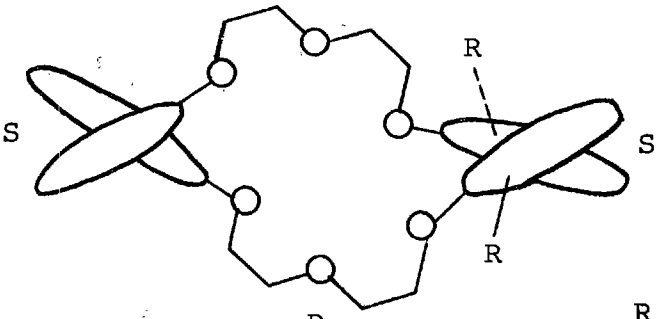


(S, S) - 5a $\frac{R}{H}$ (R, R) - 6a $\frac{R}{CH_3}$

(R, R) - 5b H (R, R) - 6b CH_3

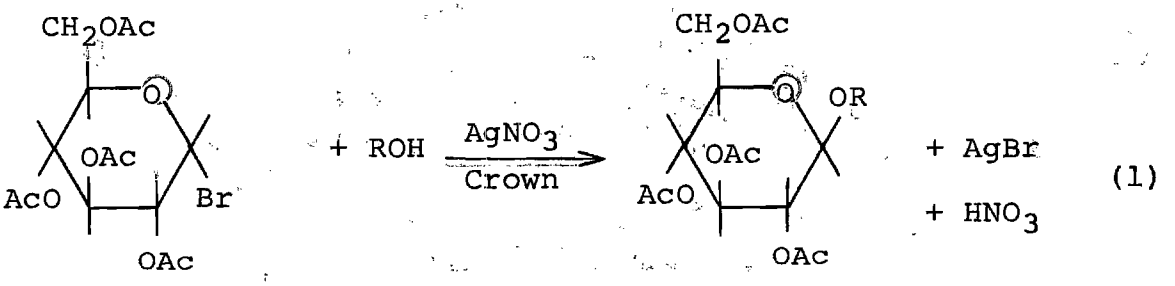
Optically pure host compounds 5 and 6 have been utilized to complex selectively the enantiomers of α-amino ester and hexafluorophosphate salts as guest compounds (these have been made extractable from H_2O into $CHCl_3$), hence demonstrating the feasibility of designing host compounds to resolve optically active amino esters by selective complexation.[54]

In another paper concerning amino esters, Cram et al.[55] have reported a method for the complete optical resolution of racemates of primary amino salts, particularly those of amino esters, by highly structured complexation of guest compounds.

Cram et al.[56] also reported that enantiomer differentiation occurs when designed, neutral, lipophilic, and chiral host compounds carry amino ester salts (guest compounds) from one aqueous solution through bulk chloroform to a second aqueous solution. Entropy of dilution and inorganic salt "salting out" of the organic salt provided the thermodynamic driving force for transport. Rate constants for transport were measured for the faster-moving enantiomer as well as for the slower-moving enantiomer.

Following a series of publications about resolution through chiral complexation,[55-60] Cram recently reported chromatographic optical resolution through chiral complexation of salts of α-phenyl ethylamine, phenyl glycine esters and of tryptophan esters.[61]

Knochel, Rudolph, and Theim[62] reported the use of dibenzo-18-crown-6 in the reaction of an acetylated halo-sugar, 7, with a series of alcohols catalyzed by silver nitrate (reaction 1). This Koenigs-Knorr reaction proceeds in good yield with inversion of configuration.



7 8 (1)

The Koenigs-Knorr reagents ($AgNO_3$ with ROH) have been utilized with dibenzo-18-crown-6 and halide substrates to synthesize glucosides in 1-5 minutes at room temperature in yields between 43-81%. Of the alcohols studied, methanol gave the highest yield while cyclohexanol gave the lowest yield.

Cationic Complexes of Crown Ethers

The term polydentate ligands is appropriately associated with crowns and cryptates along with oxa, aza, thia and mixed crowns. These multidentate ligands can specially complex alkali cations. The complexation is greatest when oxygen is incorporated in the crown ring. When nitrogen or

sulfur is substituted for oxygen in the crown, however, the affinity of crown ethers to complex alkali metal cations is greatly reduced except for Ag(I) ion where the complexing affinity is increased or unaffected in most cases.[7, 9, 16]

Pedersen attributed crown ether complexation with alkali metal cations to ion-dipole interactions between the cation and the negatively charged oxygen atoms which are symmetrically arranged in the polyether ring (Figure 1).

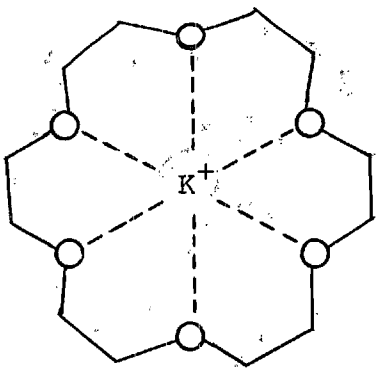
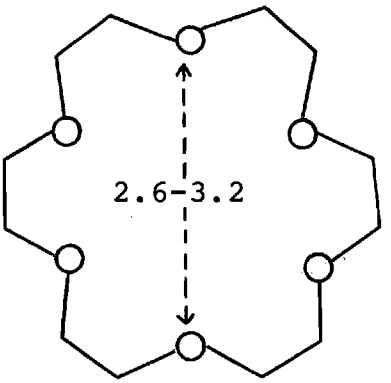
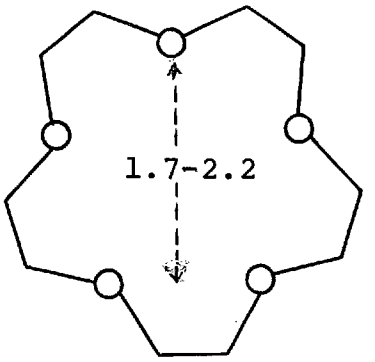


Figure 1. 18-crown-6 Complexation with Alkali Metal Cations (e.g., K^+).

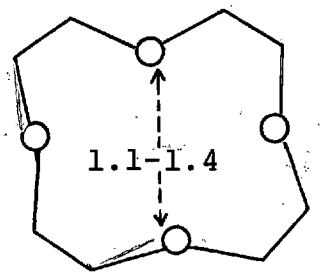
An interesting finding in this regard was that the potassium ion was the best fit among the alkali metal cations for the cavity in 18-crown-6. Similarly, it was found that 15-crown-5 and 12-crown-4 have the best cavity sizes for accommodating sodium and lithium ions, respectively. This conclusion was based upon the ionic radii of the various alkali metal cations and the diameters of the respective crown ether cavities (Figure 2).



18-Crown-6



15-Crown-5



12-Crown-4

	Ionic Diameters
K^+	2.66
Na^+	1.94
Li^+	1.36

Figure 2. Structures of 18-Crown-6, 15-Crown-5 and 12-Crown-4 with an Estimate of Their Respective Cavity Diameters and the Ionic Diameters of Some Simple Alkali Metal Cations (e.g., K^+, Na^+ and Li^+).

Though 18-crown-6 has been reported to solubilize sodium salts, it should be emphasized, however, that 18-crown-6 is more specific for the potassium cation than for the sodium cation. Likewise, the lithium cation is more specific for 12-crown-4 than for either 15-crown-5 or 18-crown-6.

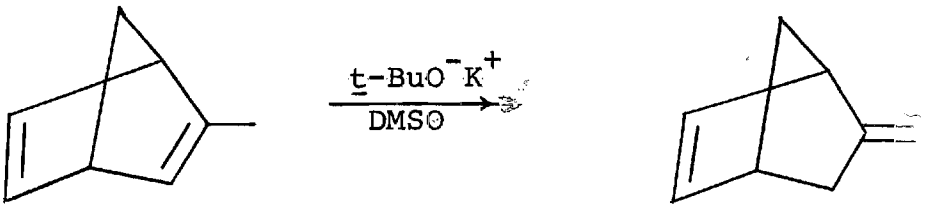
Cationic complexes of crown ethers were first reported by Pedersen.[1-11] Complexes were formed by mixing different proportions of crown and salt in methanol at 60°C to effect solution. The solutions were then left to cool at room temperature whereby cationic complexes of crown ethers would precipitate out. Utilizing elemental analyses, crown:salt stoichiometric ratios of 1:1, 2:1, and 3:2 were obtained. Pedersen postulated that the 2:1 and 3:2 complexes were in a "sandwich" configuration. Since then, x-ray crystallography has been utilized to elucidate the pattern of crown-salt complexes.[63-65]

The solution chemistry of crown ether-metal cation complexes has also been studied by potentiometry,[7,9,16] specrtophotometry,[66-68] calorimetry,[13g,69,70] distribution equilibria,[71] ESR,[72,73] paper chromatography,[37] nmr,[74-77] conductance measurements,[78] and uv spectroscopy.[18, 30] Other complexes of crown ethers besides the metal cation complexes have also been reported.[32,51]

Su and Weiher[18] have reported the complexation of dicyclohexyl-18-crown-6 with transition metal cations including Ti^{+3}, V^{+3}, Fe^{+3}, Co^{+2} and Zn^{+2}. Dicyclohexyl-18-crown-6 complexation with Co^{+2} was also reported by Birbeck et al.[34] Recently, crown complexes of rare earth metals have been reported.[79-80]

18-Crown-6 was found to form solid 1:1 complexes with potassium tosylate, potassium thiocyanate, sodium thiocyanate[81] and potassium cyanide, acetate, etc. 16-Crown-4 formed solid 1:1 complexes with LiBr and LiI and solid 2:1 complexes with LiSCN.[82] 12-Crown-4 formed solid 1:1 complexes with LiI and a solid 2:1 pentahydrate complex with NaCl.[44]

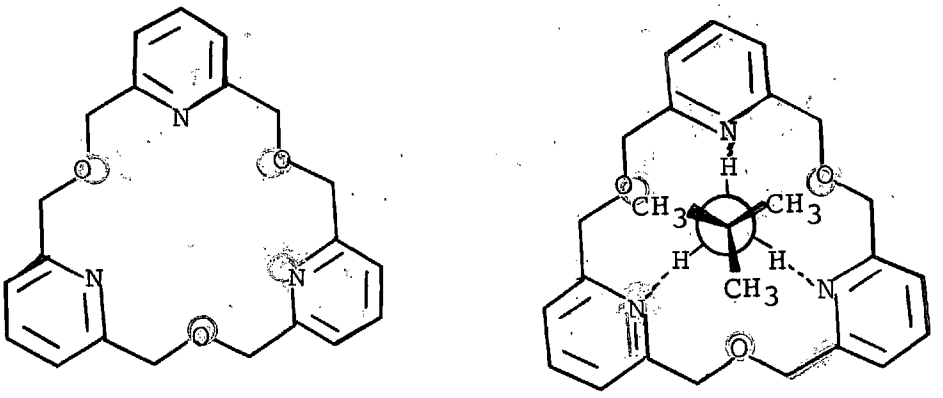
The exceptional complexing ability of 18-crown-6 was proved by Maskornick[83] who determined the rate of isomerization of 2-methylbicyclo [2.2.1] hepta-2, 5-diene, 9, to 5-methylenebicyclo[2.2.1]hept-2-ene, 10, by t-Bu^-OK^+ in DMSO (Reaction 2). At low concentrations (ca. 0.1M) of t-BuO^-K^+, the reaction showed variable order base dependence, approaching first order at high dilution, while at higher concentrations, zero order base dependence was observed. With catalytic 18-crown-6, however, the kinetics followed first order base dependence from 0.01M to 0.33M t-BuO^-K^+. Thus, at low concentrations in DMSO alone, some solvent-separated ion pairs are present, while at higher concentration, ionic aggregation began to appear thus zero order base dependence was observed. With the crown present, however, solvent-separated ions were maintained to a higher level of base concentration. Thus, it was concluded that crown dramatically improved the activity of potassium alkoxides even in highly solvating media as DMSO.



(2)

9 10

Regarding the synthesis of host and guest compounds, a series of publications have appeared by Cram et al.[55-59,61,84,85] It has been reported that compound 11 strongly complexes with tetrabutylammoniumthiocyanate and forms a crystalline 1:1 complex 12 (molecular models suggest this structure).

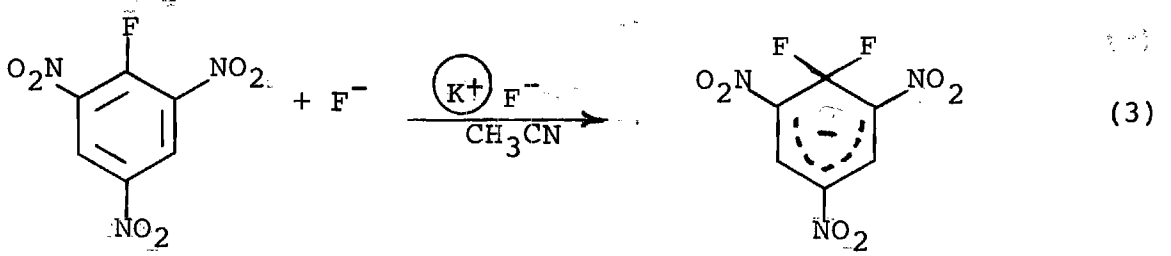


11 12

Cram[51] reported the complexation of 18-crown-6 with p-toluenediazonium tetrafluoroborate. Cram also postulated the complex involved insertion of the linear $-N^{+}{=}N$ group into the whole of 18-crown-6 based on PMR shifts.

No crown-nitrile complex had been synthesized until the recent discoveries of Harris and Liotta who reported a high melting crystalline complex of 18-crown-6 and acetonitrile.[14, 15] Following that, Henson reported the isolation of three novel non-metallic 18-crown-6 complexes. Cyanogen bromide, malonitrile, and succinonitrile formed 2:1 (nitrile to 18-crown-6) stoichiometric complexes. The cyanogen bromide complex was not stable while the malonitrile and succinonitrile complexes were stable melting at 127-129°C and 83-84°C, respectively.[86]

Terrier, Ah-Kow, Pouet, and Simonnin[87] have detected the formation of sigma anionic complex (Meisenheimer complex) using ^{1}H and ^{19}F-nmr spectroscopy. This complex, 14, was formed by adding picryl fluoride, 13, to a heterogeneous mixture of 18-crown-6 and potassium fluoride in CH_3CN (Reaction 3).



(3)

13 14

Phase-Transfer Catalysis, Solvation, Solubility, and Nucleophilicity

Reactions between two substances located in different solvent phases are often inhibited by the inability of reagents to come together. Tetraalkylammonium salts, crown ethers, and to a lesser degree, tetraalkylphosphonium salts have proved suitable to transfer anions from one phase to another. The drastic increase in the rate of some reactions is due to two factors: first, the reacting anion, which is normally water soluble, is made more soluble in the organic phase by the phase-transfer catalyst. The hydrophobic carbon chains of the ammonium complex are responsible for its solubility in the organic phase. Secondly, especially in the case of the crown ethers where the cation is complexed, the anion exists as a "naked" anion, without being solvated, and is therefore especially reactive.

The solubilization and phase-transfer effects of crown ethers have been subjected to intensive study in the last few years. To mention a few, Dye, DeBacker, and Nicely[32] formed stable solutions of K and Cs metal in THF-dicyclohexyl-18-crown-6 solutions at room temperature, and of potassium with diethyl ether-crown at -78°C. The use of dicyclohexyl-18-crown-6 resulted mainly, however, in the formation of metal anions.

Kaempf, Lehn, and coworkers[88] studied the dissolution of alkali metals in benzene and toluene.

Starks, utilizing quaternary ammonium and phosphium salts[89-91] as phase-transfer catalysts, studied the cyanide nucleophilicities in liquid-liquid phase-transfer processes (Figure 3). Starks reported excellent yields for the conversion of primary and secondary alkyl halides to alkyl cyanides.[89a-b] The conversion, however, failed when activated halides (allylic and benzylic) were used and hydrolysis to the alcohol, not displacement by cyanide, was the principal product. This disadvantage has been overcome by using 18-crown-6 as a phase-transfer catalyst in solid-liquid phase-transfer processes (Figure 4).[92-111] Moreover, with this technique at hand, it is possible to carry out nucleophilic displacements on substrates which react with nucleophilic solvents (H_2O, ROH or DMSO).

(a)

$$NR_4^+ X^- + OH^- = [NR_4^+ OH^-] + X^- \qquad \text{Aq. Phase}$$

$$[NR_4^+ OH^-] + H\,Sub = [NR_4^+ Sub^-] + H_2O \qquad \text{Interface}$$

$$[NR_4^+ Sub^-] + R^1X = [NR_4^+ X^-] + R^1Sub \qquad \text{Org. Phase}$$

(b)

$$NR_4^+ X^- + Y^- = [NR_4^+ Y^-] + X^- \qquad \text{Aq. Phase}$$

$$[NR_4^+ Y^-] + R^1X^- = [NR_4^+ X^-] + R^1Y \qquad \text{Interface / Org. Phase}$$

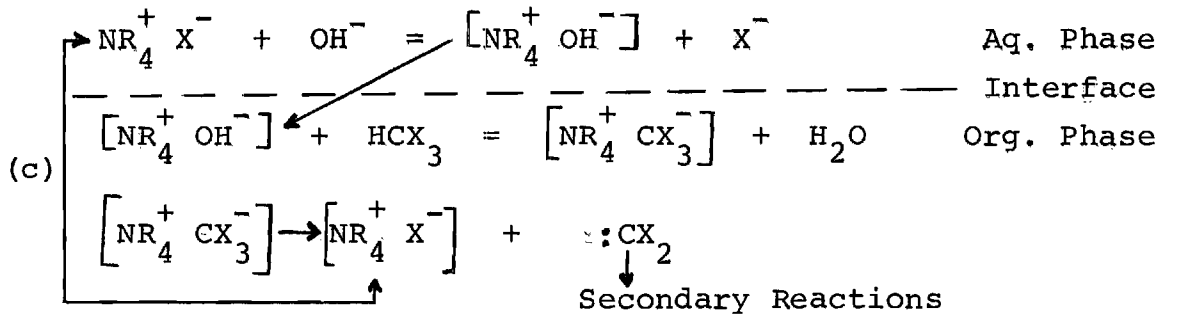


Figure 3.[89d] Course of Liquid-Liquid Phase-Transfer Catalysis by Quaternary Salts. Ion Pairs are Enclosed in Square Brackets.

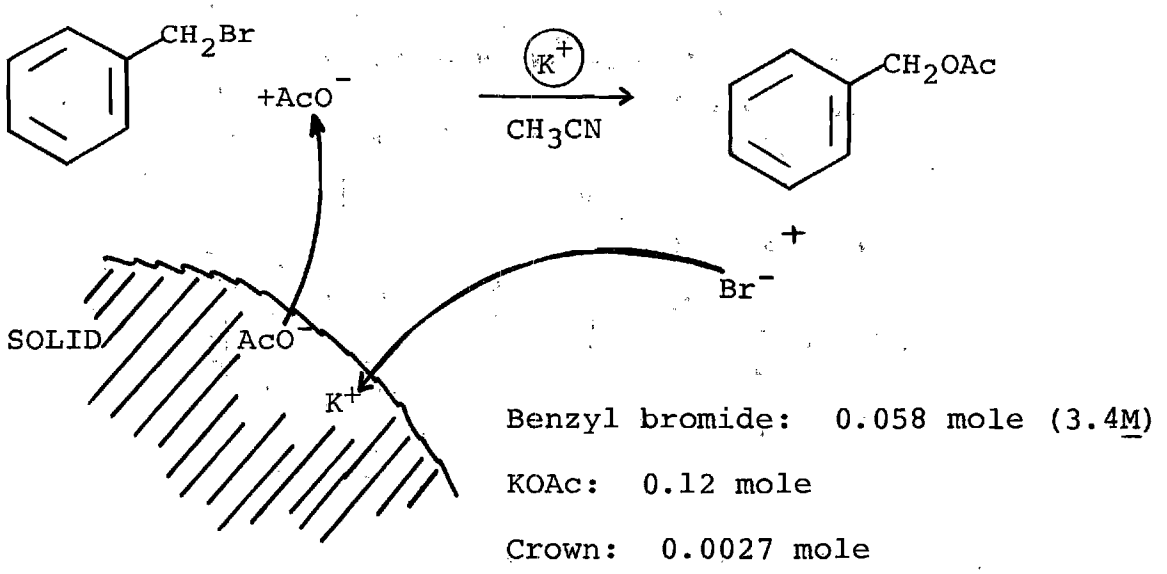


Figure 4. Course of Solid-Liquid Phase-Transfer Catalysis by Crown Ethers.

As can be seen in Figure 3, small quantities of catalyst are needed to transfer one reactant across the interface into the other phase so that reaction can proceed. The

phase-transfer agent is not consumed but performs the transport function repeatedly. Organic soluble quaternary ammonium, NR_4^+, or phosphonium cations, PR_4^+, were found to be excellent agents for the transport of anions from an aqueous phase to an organic phase. Hence, alkylation of nitriles,[89d] aromatics, etc., in the presence of aqueous NaOH and ammonium salt can be interpreted as in Figure 3(a). Displacement reactions[89a,d] such as the reaction between cyanide and chlorooctane can be interpreted as in Figure 3(b). Likewise, generation of dihalocarbenes[89d] from aqueous NaOH, ammonium salt, and haloform can be interpreted as in Figure 3(c).

A simplistic view of the solubilization process by 18-crown-6 may be visualized by Figure 5. The 18-crown-6 is of the proper dimensions such that it can effectively coordinate with a potassium ion. Since the complex has a hydrophobic ("greasy") exterior (Figure 5), it is readily solubilized by the non-polar or dipolar aprotic solvents. The anion which accompanies the potassium-crown complex into solution is a potent nucleophile and a potent base and is not expected to be highly solvated in benzene or acetonitrile, aprotic solvents that have a poor affinity for the anion. These specific anions have been termed "naked" anions.[12]

The solubilization of alkali metal salts in crown ethers in non-polar and dipolar aprotic solvents depends largely on the crystal lattice free energy of the salt (ΔG_1), the free energy of complexation of the metal ion by the

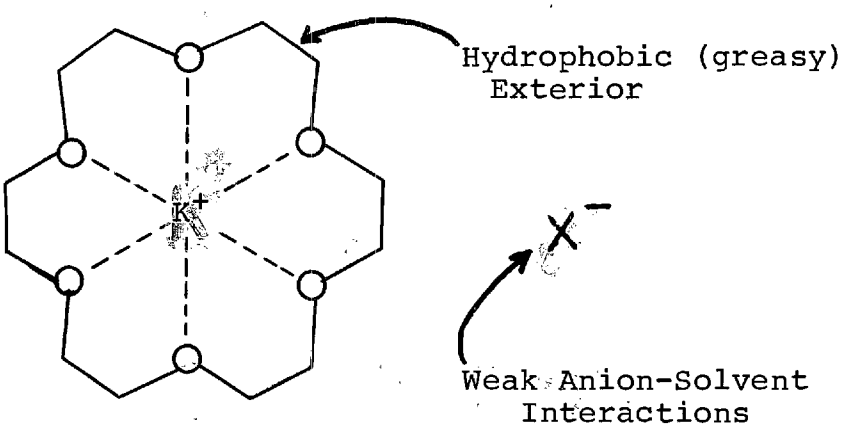


Figure 5. Solubility of Potassium Salts in Non-Polar and Dipolar Aprotic Solvents.

crown in the gas phase (ΔG_3), and the free energy of solution of the anion (ΔG_5) (where ΔG_2 is the free energy of solution of the crown and ΔG_4 is the free energy of solution of the metal crown complex. (See thermodynamic cycle, Figure 6.)

$$\begin{array}{ccc} \text{Crown (gas)} + K^+ \text{(gas)} + X^- \text{(gas)} & \xrightarrow{\Delta G_3} & K^+\text{—crown (gas)} + X^- \text{(gas)} \\ \uparrow \Delta G_2 \qquad \uparrow \Delta G_1 & & \downarrow \Delta G_4 \qquad \downarrow \Delta G_5 \\ \text{Crown (sol'n)} + KX \text{ (solid)} & \longrightarrow & K^+\text{—crown (sol'n)} + X^- \text{(sol'n)} \end{array}$$

Figure 6. Thermodynamic Cycle for the Solubilization Process of a Metal Ion Salt in Crown-Solvent System in the Hypothetical One Molal Infinite Dilution State.

Harris and Liotta[94] determined the solubility of KOAc in 0.14M 18-crown-6-CH_3CN solution by nmr techniques and found the solubility to increase by a factor of 200 in

the presence of 0.14M crown (Appendix 1). Knochel, Oehler, and Rudolph[101] have also reported the solubility of potassium acetate in acetonitrile in the presence of a variety of macrocyclic polydentate ligands.

Liotta, Grisdale, and Hopkins[112] utilizing kinetic and conductance techniques have arrived at the following order of nucleophilicities $N_3^- \geq OAc^- > CN^- > F^- > Cl^-, Br^- > I^- > SCN^- >>$ thiourea. This order was determined by reacting the potassium salt of each anion ("naked" anion) with benzyl tosylate in catalytic 18-crown-6-acetonitrile solution at 30°C. The authors have also shown that "naked" anions in acetonitrile are solvated by much weaker forces than in protic solvents.

Landini, Montanari, and Pirisi[99] have reported the reactions of a series of octyl derivatives with a variety of potassium and sodium halides under liquid-liquid phase-transfer catalytic conditions using dicyclohexyl-18-crown-6 as the phase-transfer catalyst. The following conclusions could be drawn from their data: the relative nucleophilicities of halide ions is $I^- > Br^- > Cl^- > F^-$; secondary substrates react slower than primary substrates and sodium and potassium salts react at about equal rates. It is interesting to note that this nucleophilicity order is reversed when going from protic to dipolar aprotic solvents.[113-122] Moreover, the order of reactivity follows the basicity of the nucleophiles, the most reactive being the most basic, except

for the cyanide ion which falls between acetate and fluoride ions. This may be due to increased solvation of the cyanide ion due to interaction with the cyano group of acetonitrile (Figure 7).

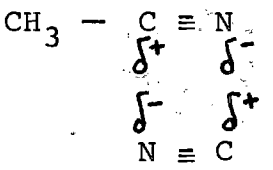


Figure 7. Solvation of the Cyanide Ion with the Cyano Group of Acetonitrile.

Crown ethers have been used as addends to investigate the ion-pair processes of fluorenyl salts in solution. The crown ethers were found effective in converting contact-ion pairs to solvent-separated ion pairs and thus increasing ion-pair dissociation in a variety of solvents.[67, 68, 123-132] Crown ethers have therefore been used as addends in elimination reactions as a means to determine the effect of base association in these reactions.[123-136]

Crown Ethers as Reagents and Catalysts

Crowns were utilized in synthetic reactions as early as 1970 when Fraenkel and Pechhold studied the decomposition of phenylazoformate salts, 15, and the alkoxide cleavage of benzoyl-tert-butyl diimide, 16, in the presence of dicyclohexyl-18-crown-6 (reactions 4 and 5, respectively).[43] It

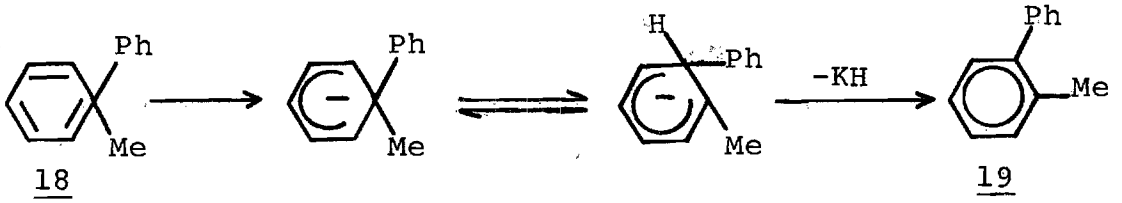
is worth mentioning that both decomposition cases occurred *via* the diimide route (Reaction 6). Thus the authors were able to effect solubilization of the normally insoluble substrates in benzene *via* crown complexation.

$$\underset{\underline{15}}{\Phi N = N\text{-}CO_2^-} \longrightarrow \Phi^- + N_2 + CO_2 \qquad (4)$$

$$\underset{\underline{16}}{\text{+}N = N\text{-}C(=O)\text{-}\Phi} + OR^- \longrightarrow \text{+}^- + N_2 + \Phi CO_2R \qquad (5)$$

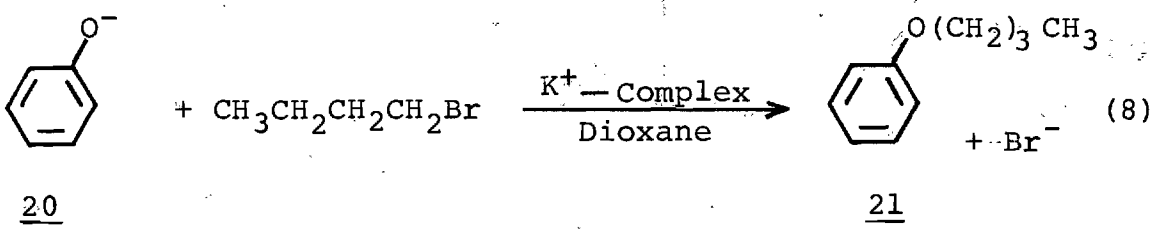
$$\underset{\underline{17}}{RN = N^-} \longrightarrow R^- + N_2 \qquad (6)$$

Staley and Erdman[124] studied the decomposition of 6-methyl-6-phenylcyclohexadienyl anion formed from 5-methyl-5-phenyl-1,3-cyclohexadiene, 18, with metal amides in liquid ammonia. They found that $LiNH_2$ gave a much higher yield of 2-phenyl toluene, 19, than did KNH_2. When dicyclohexyl-18-crown-6 was added to the KNH_2 system, however, the yields were identical. It was, therefore, concluded that the decomposition of the anion was greatly influenced by complexation of crown ether with the counter ion (Reaction 7).[125]



18 19 (7)

Roitman and Cram[126] found that t-BuO^-K^+ in t-BuOH showed a much greater kinetic basicity in the presence of 18-crown-6. Thomassen and coworkers[127] found that addition of catalytic amounts of dicyclohexyl-18-crown-6 greatly increased the rate of alkylation of potassium phenoxide, 20, with butyl bromide in dioxane (Reaction 8). They also found that the rate of reaction reached a maximum when 18-crown-6 was used but when linear polyethers were substituted for the crown, the reactivity of the phenoxide was vastly reduced.



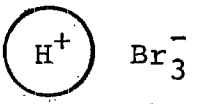
(8)

20 21

Sam and Simmons[93] reported the solubilization of $KMnO_4$ in benzene by complexation with dicyclohexyl-18-crown-6 and used the resulting solution as an oxidizing agent for olefins, alcohols, aldehydes, and alkyl benzenes. These oxidations gave quantitative yields of products under mild conditions and thus the reagent was postulated as having a great synthetic utility.

Schori and Jagur-Grodzinski[137] explored the effect of added dicyclohexyl-18-crown-6 on the kinetics of bromination of stilbene in the absence and in the presence of HBr using solvent chloroform. In the absence of HBr, added crown

resulted in a slight increase in the reaction rate, presumably due to traces of HBr formed *in situ*. In the presence of excess HBr, however, added crown strongly inhibited the reaction. This was attributed to the tieing up (binding) of the bromine in a crown-tribromide complex, 22, that was less reactive toward the stilbene (the crown ring represented as a circle):



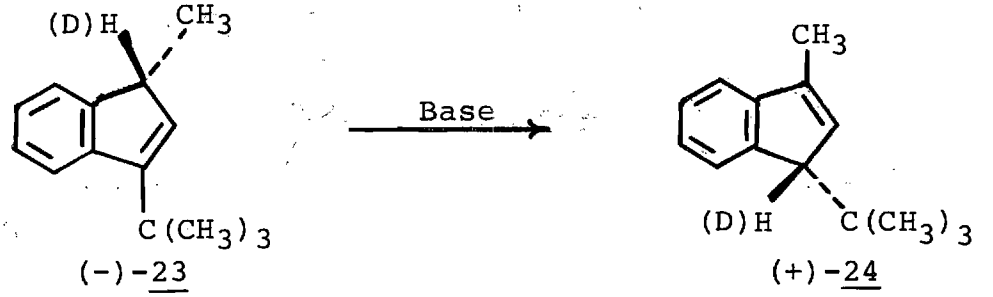
22

Crown ethers have also been reported as effective additives in the reduction of ketones with $NaBH_4$ in aromatic solvents.[138] Matsuda and Koida[138] reported the reduction of ketones with $NaBH_4$ in dibenzo-18-crown-6-aromatic solvent systems. Crown addition dramatically increased the yield of alcohol (the yield was also increased with increasing crown concentration) over diglyme and DME addition.

Durst and coworkers[139] reported 90-100% isolated yields of phenacylesters with catalytic dicyclohexyl-18-crown-6 (potassium acetate and p-dibromoacetophenone in refluxing CH_3CN, 15 minutes).

Selective reductions of sulfoxides with sodium cyanohydridoborates (mixed solvents of CH_2Cl and alcohol, 58-92% isolated yields) have also been reported.[140]

Cram, Almy, and Garwood,[125] in a continuation of earlier studies, investigated optically pure 3-tert-butyl-1-methylidene-1-H (1-D), 23, racemization, isotopic exchange, and isomerization to 1-tert-butyl-1-methylidene, 24, in various media and it was revealed that addition of catalytic dicyclohexyl-18-crown-6 in 75% benzene-25% phenol-potassium phenoxide medium sharply reduced the stereospecificities of the isotopic exchange reaction, isomerization reaction, and particularly the exchange rearrangement reaction. With methanol-O-d-potassium methoxide and in THF-n-propylamine-N-d_2 solvent, crown ether had only a minor effect on the rates of isomerization (Reaction 9).



(-)-23 (+)-24 (9)

Generation of Carbenes

Starks[89a] and Green[19] have also utilized crown ethers in the generation of diazomethane and their subsequent synthetic utilization in synthesis.

Sepp, Scherer, and Weber[140] reported the generation of diazomethane with hydrazine hydrate-chloroform-potassium-

hydroxide-catalytic 18-crown-6 in ether (48% yield). The yield decreased to 35% on using sodium hydroxide.

Makosza and Ludwikow[141] found dibenzo-18-crown-6 an effective additive in many reactions of carbanions and halocarbenes, including alkylation of C-H acids, reactions with trichloromethyl anion and dichlorocarbene, reactions of carbanions with aromatic nitro compounds, and Darzens condensations. Phenyl halocarbenes were generated from benzal halides with $\underline{t}$-BuO^-K^+ and catalytic 18-crown-6.[106] Omission of 18-crown-6 resulted in elimination from the dihalide to give phenyl carbenoids. Dichlorocarbene was generated from chloroform and the base with or without 18-crown-6; olefin reactivities were higher for the former case, however.

Use of 18-crown-6 ether in the rearrangement of organoalkali compounds such as 2,2,3-triphenyl propyl lithium was reported by Grovenstein.[142] It was found that the use of 18-crown-6 ether in the presence of $\underline{t}$-BuO^-K^+ and THF at -75°C for 30 minutes selectively directs a 1,2-migration of benzylanion to give 100% (this is relative mole percent) of $Ph_2\ddot{C}^-M^+CH_2CH_2Ph$, 25, while in the absence of crown ether and under exactly the same conditions the product distribution is 63 relative mole percent of 25 via 1,2-benzyl anion migration and 37 relative mole percent of 26 formed via 1,2-phenyl anion migration $PhCH_3\overset{Ph}{\overset{|}{\ddot{C}}}{}^-M^+CH_2Ph$, 26.

Landini, Montanari, and Pirisi[99] have reported the use of dicyclohexyl-18-crown-6 ether as a phase-transfer catalyst in anion promoted two-phase reactions. These workers also reported that

> crown ethers, with a suitable structure, can be effectively used in catalytic amounts in two-phase organic aqueous systems. In these conditions they act as phase-transfer catalysts, provided that aliphatic chains are bonded to the molecule so as to secure a partitioning of the crown ether-salt complex between the two phases.[99]

They further reported the displacement reactions of the unsolvated anions: I^-, Br^-, CN^-, Cl^-, and F^- on n-octyl (-tosylate, -bromide or -iodide) and that the apparent nucleophilicity scale was $I^- > Br^- > Cl^- > F^-$.

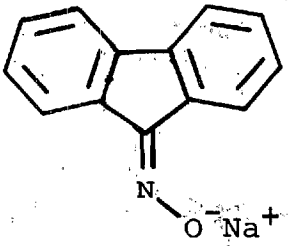
Smid has reported that bathochromic shifts caused by the addition of crown ethers to a solution of alkali picrates in THF can be rationalized in terms of tight and loose ion-pair-crown ether complexes.[143] Also, conductance measurements showed that the fraction of free ions was always less than 0.1. Crown ethers used were dimethyldibenzo-18-crown-6, monobenzo-15-crown-5, and a bis-crown ether of 15-crown-5.

Literature Review of the Utility of Crown Ethers in Substitution, Addition, and Elimination Reactions

Substitution Reactions

Crown ethers have been utilized in nucleophilic substitution reactions. The reaction of sodium 9-fluorenyloximate, a bidentate, structure 27 with methyl iodide in a

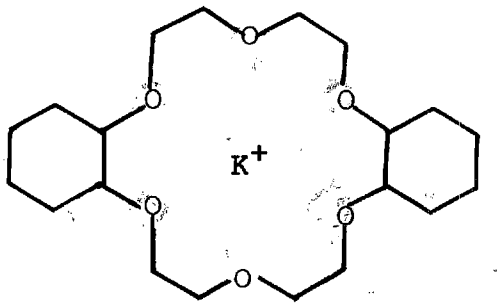
mixture of solvents, CH_3CN and t-BuOH, gives alkylation at both oxygen and nitrogen. Addition of dibenzo-18-crown-6 to the reaction mixture, however, caused increased rates of reaction and higher fractions of oxygen alkylation indicative of increased dissociation of the salt in solution.



27

Sam and Simmons,[97] in an interesting paper, reported enhanced reactivity of alkali salt-crown complexes 28 and 29 in acetone in nucleophilic substitution and elimination reactions. They also reported surprisingly facile, nucleophilic aromatic substitution of $KOCH_3$-crown complex 30 in aromatic hydrocarbons (Reaction 10). Hence, in the presence of crown, the solubilized OCH_3^- underwent unprecedented aromatic substitution with dichlorobenzenes to give monochloroanisoles in good yields under mild conditions with no reaction occurring in the absence of crown ether (Reaction 11).

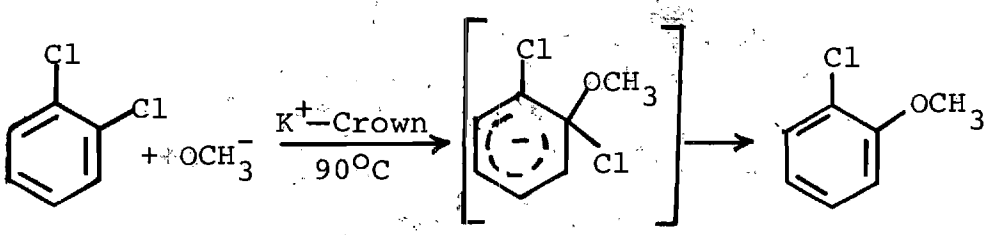
In addition to the observations of Sam and Simmons,[97] reaction of pure crystalline complexes of 28 and 29 with n-butylbrosylate in acetone at 25°C gave clean second order



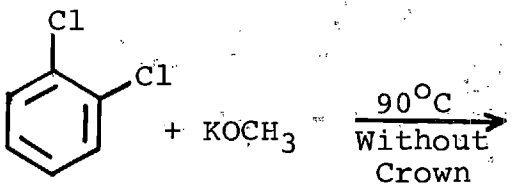
28. $X^- = Br^-$

29. $X^- = I^-$

30. $X^- = OCH_3^-$



(10)



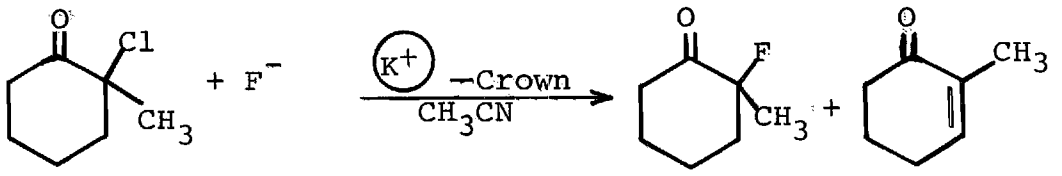
(11)

nucleophilic substitution kinetics. Because of the insolubility of KBr in acetone, little or no reaction occurs in the absence of crown complexation.

Durst[104] has reported the displacement reactions of "naked" nitrite anions in methylene chloride containing 18-crown-6 with primary alkyl halides to form nitro compounds as the major product, the major bi-products being nitrite esters (Reaction 12).

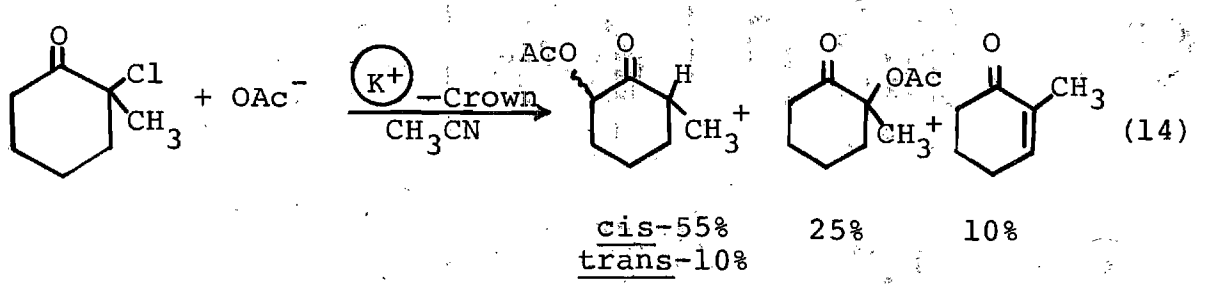
$$CH_3(CH_2)_6CH_2Br + NO_2^- \xrightarrow[CH_2Cl_2]{K^+-Crown} CH_3(CH_2)_6CH_2NO_2 \quad 65\text{-}70\% \qquad (12)$$

Liotta and Harris[94] have reported the solubilization of potassium fluoride in acetonitrile and benzene containing 18-crown-6 and the reactions of this solubilized fluoride, which they have termed "naked" fluoride, with a variety of organic substrates. They demonstrated the following reaction types: (i) displacement reactions at sp^3 hybridized carbon with leaving groups located at primary, secondary, tertiary, and benzylic positions; (ii) competing elimination processes; and (iii) displacement reactions at sp^2 hybridized carbon. Also, reaction conditions were relatively mild and the conversions essentially quantitative. Less than 5% reaction took place in the absence of crown ether under identical conditions covering the same periods of time (Appendix 1). An interesting reaction which illustrated the competition between displacement and elimination processes was the reaction of "naked" fluoride with 2-chloro-2-methylcyclohexanone, a substrate subject to "Favorskii" rearrangement products, producing 2-fluoro-2-methylcyclohexanone and 2-methyl-2-cyclohexenone (Run 5, Appendix 1) (Reaction 13).



(13)

In another publication, Liotta et al.[95] reported that acetate ion solubilized as the potassium salt becomes sufficiently nucleophilic to react smoothly and quantitatively, even at room temperature with a wide variety of organic substrates (Appendix 2). Thus, compared to the reaction of 2-chloro-2-methylcyclohexanone with "naked" fluoride, the reaction with "naked" acetate in acetonitrile at reflux yielded a mixture of acetates with only 10% of 2-methylcyclohexenone (Run 7, Appendix 2) (Reaction 14).



cis-55% 25% 10%
trans-10%

The authors suggested that "naked" fluoride is a stronger base than "naked" acetate.

In a continuation of earlier studies on "naked" anions, Liotta, Cook, and Bowers[96] have reported the preparation of "naked" cyanide reagent and its utilization in a variety of synthetically useful reactions. Substitution, elimination, and addition processes have been explored. It was found that "naked" cyanide is both a weak base and a potent nucleophile, and that the reagent produces nitrile compounds smoothly,

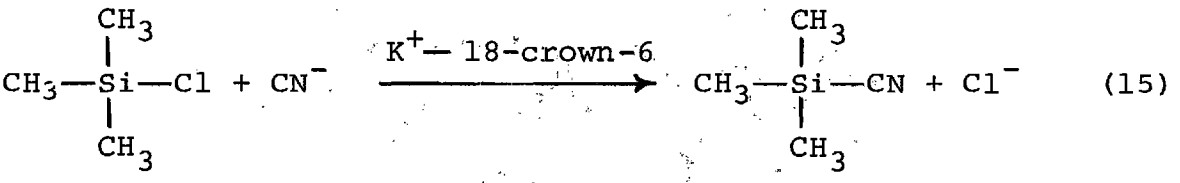
under mild conditions, and in high yields from a variety of organic substrates (Appendix 3). The reactions were carried out by simply pouring a substrate-18-crown-6 solution directly over excess, dry KCN, and stirring the two-phase system vigorously at ambient or reflux temperatures until reaction was complete. Little or no reaction was found to take place in the absence of crown under the same conditions covering the same periods of time (Runs 20 and 21, Appendix 3). In all cases, the crown was present in catalytic quantities, indicating that it behaved as a phase-transfer catalyst. In general, the reactions were more rapid in acetonitrile than in benzene and the former was determined to be the preferred solvent.

The reaction of "naked" cyanide with benzyl chloride proceeded quickly and quantitatively to product under mild conditions (Run 20, Appendix 3). With primary substituted alkyl halides, the conversions to nitrile compounds were quantitative, with no elimination products detected (Runs 1-12, Appendix 3). Displacement at secondary carbon produced primarily substitution products with only a small percentage of elimination products. These results compare favorably to those obtained with "naked" acetate,[95] but are in direct contrast to those of "naked" fluoride,[94] where large quantities of alkenes were obtained. It appears therefore that "naked" fluoride may be a stronger agent for promoting elimination processes than either "naked" cyanide or "naked" acetate.

Cyclohexyl halides gave exclusively elimination product with "naked" cyanide (Runs 17 and 18, Appendix 3). It is interesting to note that no reaction was observed with o-dichlorobenzene (Run 22, Appendix 3). This result contrasts with the reported reaction of a KOH-CH_3OH-crown system with o-dichlorobenzene to produce a 40-50% yield of o-chloroanisole.[97]

Interestingly, primary chlorides reacted at much faster rates than the corresponding bromides under the reaction conditions. For example, benzyl chloride reacted about 100 times faster than benzyl bromide at room temperature (Runs 19 and 20, Appendix 3) and 1-chlorohexane reacted about 20 times faster than 1-bromohexane at reflux temperatures (Runs 11 and 12, Appendix 3). This observation is contrary to the normally accepted leaving group order. It is also opposite to what has been observed with "naked" acetate[95] and "naked" fluoride.[94] With secondary halides, it appears that bromides react more rapidly than chlorides. For example, 2-bromooctane reacted approximately 4 times more rapidly than 2-chlorooctane at reflux temperatures (Runs 15 and 16, Appendix 3); however less alkene and a higher overall yield of substitution product was obtained with the chloride. The causes for these observations probably have their origin in the heterogeneous nature of the reaction system, the presence of catalytic quantities of crown ether, and the difference in solubility between KBr and KCl in the acetonitrile-crown medium.

Durst[104] has reported that "naked" cyanide reacts with benzyl chloride, p-nitrobenzyl chloride, p-chlorobenzyl chloride, and 3,4-dimethoxybenzyl chloride to give the corresponding nitriles in 85-90% yield. The facile displacement of "naked" cyanide in trimethylsilychloride is also reported to proceed in 45% yield (Reaction 15).

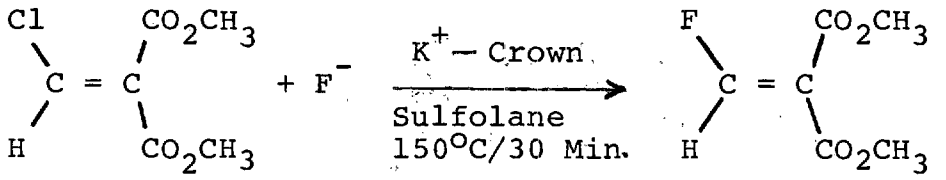


(15)

Henson[86] reported the solubilization of potassium fluoride in acetonitrile and benzene containing 18-crown-6 and the resulting "naked" fluoride, a potent base, was used to study selected Michael, Knoevenagel, and alkylation reactions. The author found the reaction times to be shorter and the yields better than those obtained in the absence of 18-crown-6 but comparable to yields obtained by other synthetic methods (Appendix 4).

Ykman and Hall[111] have reported that reaction of dimethyl-2-chloroethylene-1,1-dicarboxylate, with potassium fluoride in the presence of dicyclohexyl-18-crown-6 produces

dimethyl-2-fluoroethylene-1,1-dicarboxylate in unspecified yield (Reaction 16). Other transformations promoted by "naked" chloride are shown (Reactions 17 and 18).



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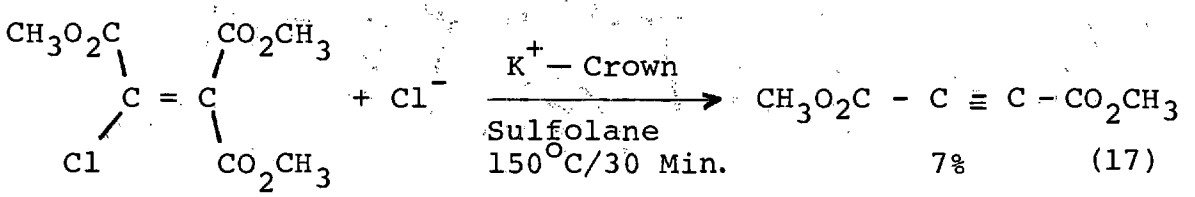

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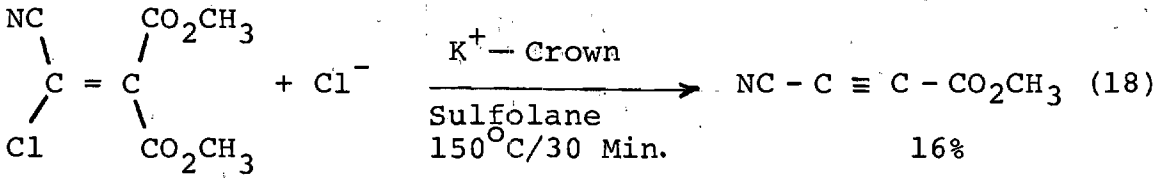
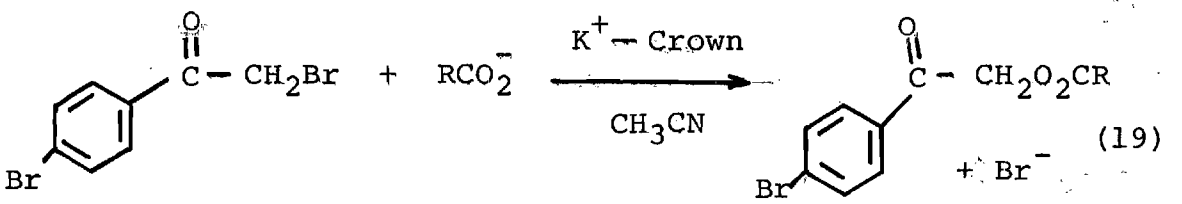


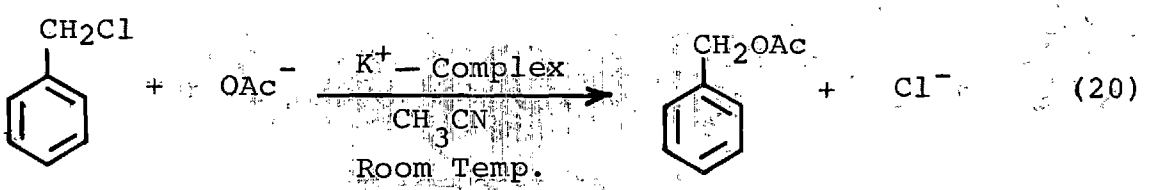
(18)

Durst[98] has reported the synthesis of a wide variety of p-bromophenacyl esters by reacting the potassium salt of a carboxylic acid with p-bromophenacyl bromide in acetonitrile and benzene using dicyclohexyl-18-crown-6 as the solubilizing agent. Ninety to one hundred percent isolated yields were reported. Moreover, reactions proceeded much faster in acetonitrile than in benzene and crown was present in catalytic quantities (Reaction 19).



(19)

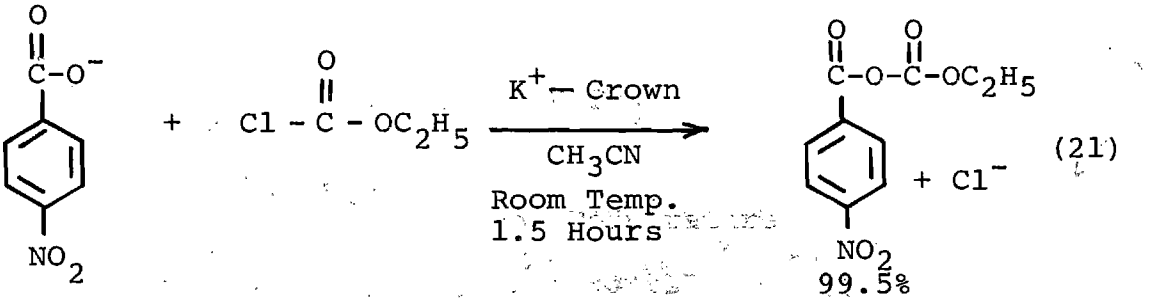
Durst et al.[144,145] have subsequently reported the formation of phenacyl esters of fatty acids in essentially quantitative yields using crown ethers as catalysts. Knochel, Oehler, and Rudolph[101] have investigated the effect of a wide variety of crown ethers on the activation of the acetate anion in its reaction with benzyl chloride in acetonitrile (Reaction 20).



(20)

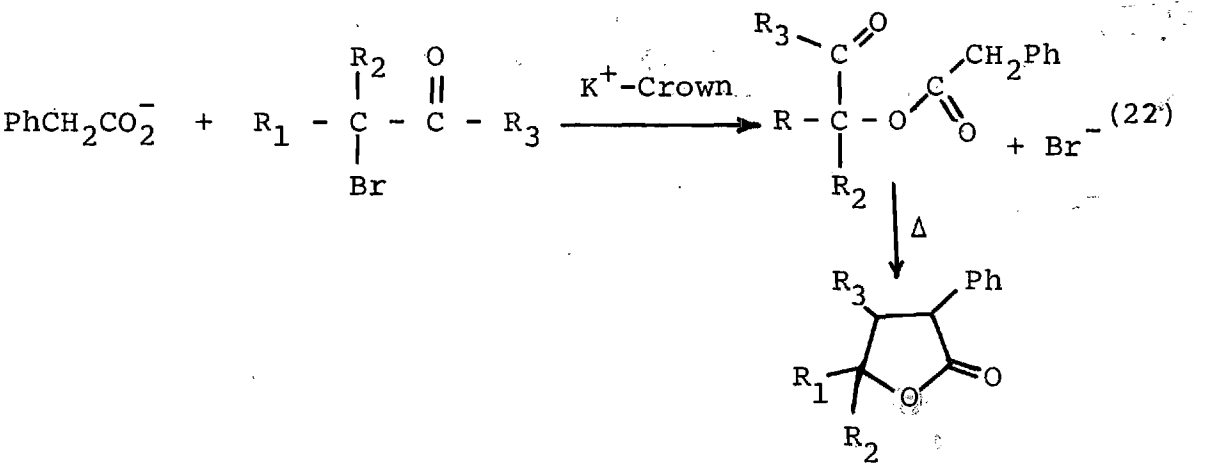
Mach, Dehm, Boden, and Durst[146] have also reported the facile synthesis of anhydrides and carbonic anhydrides from the reaction of the potassium or sodium salts of carboxylic acids with activating halide (ethylcholroformate, cyanuric chloride, and benzyl chloroformate) in acetonitrile in the presence of 18-crown-6 or dicyclohexyl-18-crown-6 (Reaction 21). In general, potassium salts were found more efficient than the corresponding sodium salts. This, as mentioned

earlier, is due to the fact that substituted or unsubstituted 18-crown-6 ethers are better complexing agents for potassium than for the sodium ion.



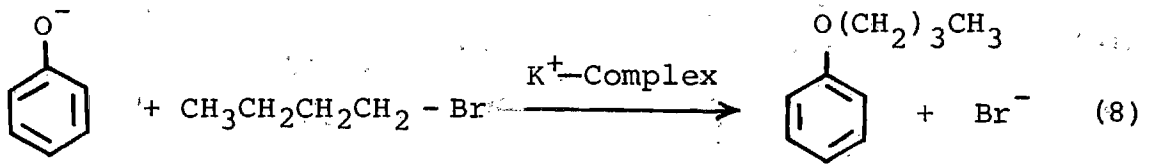
(21)

The reaction of potassium phenyl acetate with a series of 2-bromo substituted carbonyl compounds in the presence of 18-crown-6 forms aldehydro or keto esters which could be cyclized, as reported by Padwa and Dehm,[147] to a five-membered unsaturated lactone on further heating (Reaction 22).



(22)

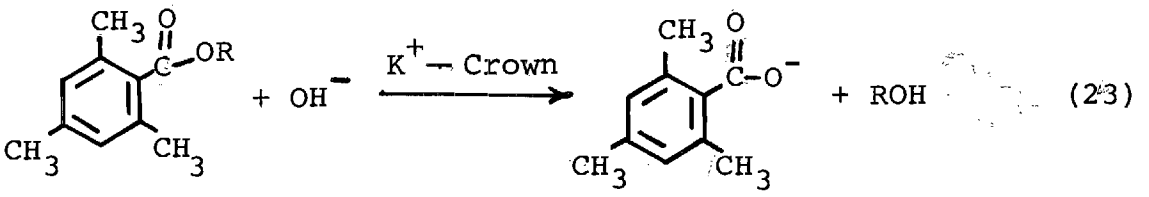
Thomassen, Ellingsen, and Ugelstad[127] have studied the rates of alkylation of potassium phenoxide with 1-bromobutane in dioxane at 25°C in the presence of a variety of linear and cyclic polyether additives (Reaction 23). All the crown ethers reported in this study increased the rate of the reaction considerably with the 18-membered crown having the greatest effect. Moreover, among the 18-membered crowns, the following rate of effectiveness was reported: dibenzo < monobenzo < dicyclohexyl. This is in the same direction as that predicted for the increase of base strength of the oxygens of the anion.



(8)

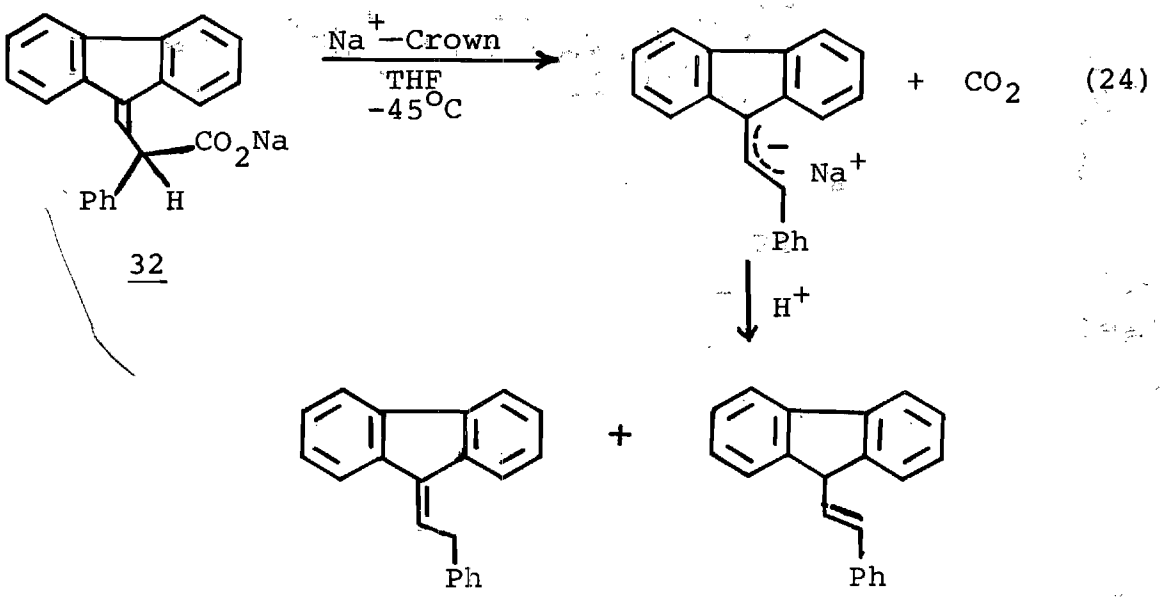
Pedersen has reported the saponification of the sterically hindered esters of 2,4,6-trimethyl benzoic acid with potassium hydroxide-dibenzo-18-crown-6 complex in aromatic hydrocarbons.[1,2,9] The reaction when carried in hydrolytic solvents gave essentially no products (Reaction 23).

Hunter, Lee, and Sims[148] have reported that at -45°C in dry THF sodium 3-(fluoren-9-ylidene)-2-phenylacrylate, 32, undergoes decarboxylation at an extremely slow rate



(23)

(i.e., essentially less than 10% reaction in 200 minutes). Addition of catalytic amounts of dibenzo-18-crown-6, however, has forced a rapid reaction ($\geq 10^5$) even at the same temperature. This would indicate that ion pairing is an important consideration in this decarboxylation reaction. The crown ether seems to coordinate effectively with the sodium ion thus producing a highly reactive "naked" carboxylate anion from the less reactive ion-paired species (Reaction 24).



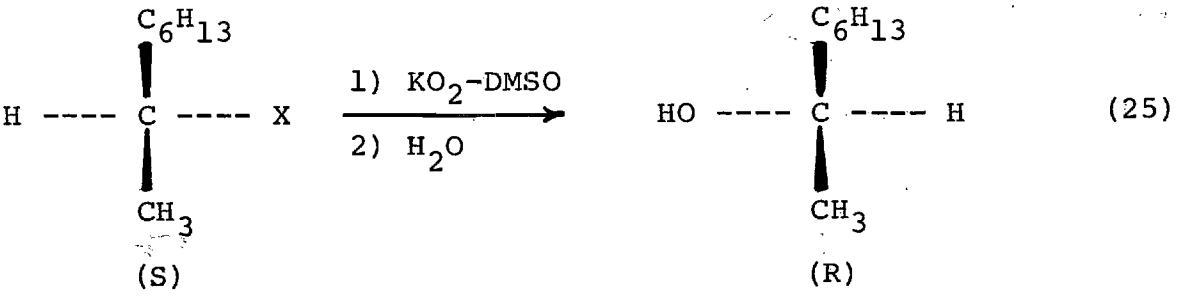
(24)

32

Recently, it has been reported that the solubility of potassium superoxide can be considerably increased in the presence of stoichiometric amounts of dicyclohexyl-18-crown-6, thus leaving the superoxide anion as a potent nucleophile.[149,150] Potassium and sodium superoxides, KO_2 and NaO_2, respectively, have previously been rejected as possible nucleophiles due to their instability in hydroxylic solvents and their insolubility in aprotic solvents.

Corey[151] has reported the solubilization of KO_2 in 18-crown-6 in a variety of solvents besides DMSO such as DMF, DME, and Et_2O. The author reported this "naked" superoxide to undergo nucleophilic displacement reactions with a variety of simple substrates to give alcohols and not hydroperoxides.

J. S. Filippo et al.[152,153] have reported that the alcohol is formed with inversion of configuration at the chiral center (Reaction 25).



(25)

Reaction of KO_2 with acyl halides to give dialkylperoxides was reported to proceed readily even in the absence of 18-crown-6 (Reaction 26).

$$2R-\overset{O}{\overset{\|}{C}}-Cl + 2KO_2 \longrightarrow RC-O-O-\overset{O}{\overset{\|}{C}}-R + 2KCl + O_2 \quad (26)$$

Following previous publications, Filippo et al.[154] reported the reaction of carboxylic esters with KO_2 in the presence of 18-crown-6 to proceed smoothly in benzene solvent to give the corresponding carboxylic acids and alcohols in excellent yields by a process that involves nucleophilic attack of superoxide at the carbonyl carbon with the subsequent formation of intermediate peroxo species (Reaction 27).

$$2RCO_2R^1 + O_2^{\cdot-} \xrightarrow[2)\ H_3O^+]{1)\ K^+-\text{Crown},\ C_6H_6} 2RCO_2H + 2R^1OH \quad (27)$$

Alpha-keto, hydroxy or halo ketones, esters, and carboxylic acids resulted in oxidative cleavage to the corresponding carboxylic acids upon reaction with "naked" superoxide (Reaction 28).

$$RC(=O)-C(=O)-R^1 + O_2^{\cdot-} \xrightarrow[2)\ H_3O^+]{1)\ K^+-\text{Crown},\ C_6H_5} RCO_2H + R^1CO_2H \quad (28)$$

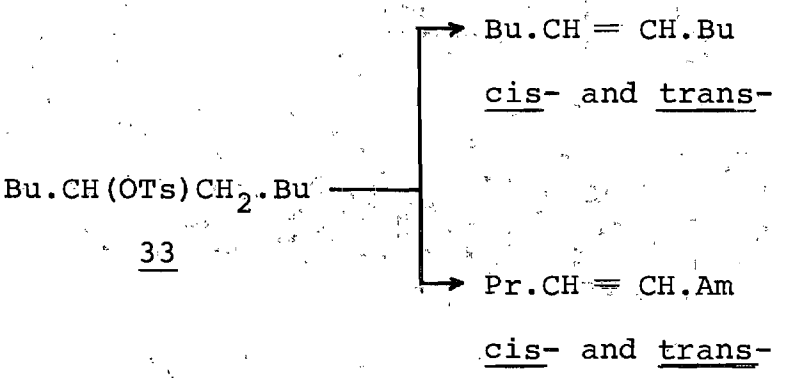
Addition-Elimination Reactions

Stereospecific and regiospecific elimination reactions on organic substrates have been the concern of a large number of workers for several decades. It has been concluded that the course of elimination reaction is dictated, to a large extent, by the state of aggregation of the basic ionic species (oxyanions and related ionic bases) which depends upon concentration, solvent, and temperature. The use of crown ethers, however, has aided in our understanding of this process.

Considering reaction (29) one finds that in solvents of low dielectric constant such as the t-BuOH ionic species exist as a combination of free ions, ion pairs and ion aggregates each of which is heavily solvated by t-BuOH. As the concentration of base increases, the state of aggregation increases and the effective size of the basic species promoting the β-elimination increases thus rationalizing the changes in the stereospecificity and regiospecificity of elimination reactions reported. Crown ether was also reported effective in breaking up ion aggregates (shifting reaction 29 to the left).

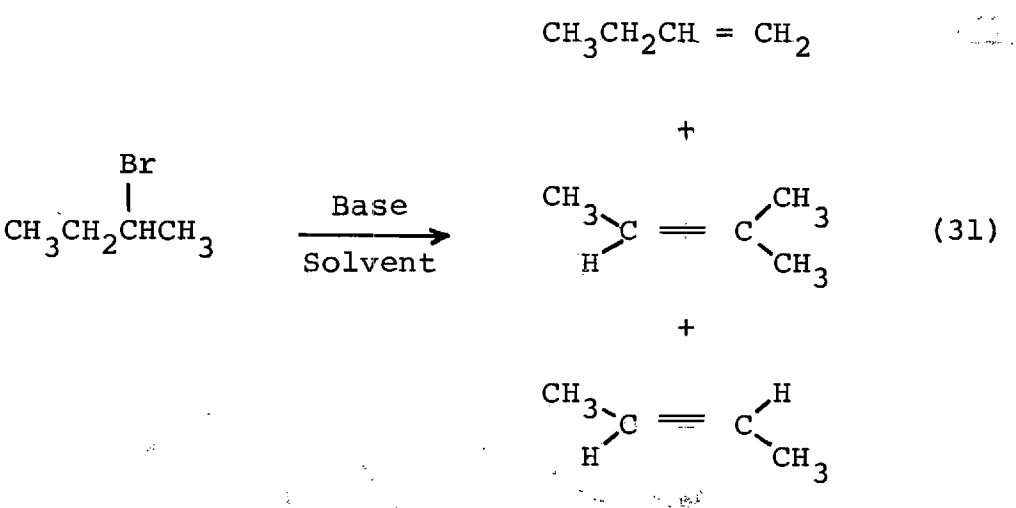
$$RO^- + M^+ \rightleftharpoons RO^-M^+ \rightleftharpoons (RO^-M^+)n \qquad (29)$$

Zavada, Svoboda, and Pankova[133] found that dicyclohexyl-18-crown-6 has led to a complete reversal of the trans- to cis- olefin ratio (trans-favored with crown) for the elimination of 5-decyltoxylate, 33, with t-BuO^-K^+ in low polar solvents. No effect, however, was exerted in dipolar, aprotic solvents. These results were attributed to a conversion from contact-ion pairs to solvent-separated ion pairs on crown complexation in low polar solvents, benzene, and t-BuOH (Reaction 30).



(30)

Bartsch [135,136,155] studied the elimination of primary, secondary, and tertiary alkoxides and found that with all alkoxides, the ratio of trans-2-butene to cis-2-butene significantly increased with crown, irrespective of the relative percentage of 1-butene. Again, the effect was attributed to increased base dissociation (Reaction 31).



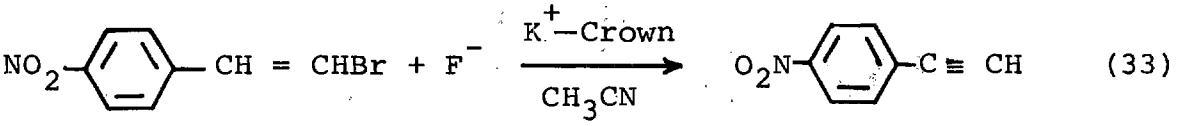
(31)

Naso and coworkers[156] studied the sterochemical course of elimination from diastereoisomeric 1-deuterio-2-fluoro-2-phenyl thioethyl phenyl sulfones. With potassium phenoxide as base, the anti-stereospecific pathway was increased dramatically at the expense of the syn- course upon addition of dicyclohexyl-18-crown-6. When sodium tert-butoxide was sutstituted as the base, however, only small changes in the two competing pathways were observed.

Borchardt and Saunders[157] studied the stereochemistry of elimination of 3-hexyltrimethylammonium iodide with potassium-tert-butoxide or n-butoxide in their precursor solvents and they found that addition of catalytic amounts of dicyclohexyl-18-crown-6 surprisingly had no significant effect on the syn-elimination. An equilibrium generating free base was postulated to prevent the crown ether from generating enough additional free base to further increase syn-elimination (Reaction 32).

$$RO^-M^+ + RNMe_3^+ + X^- \rightleftharpoons M^+X^- + RNMe_3^+ + OR^- \qquad (32)$$

Dehydrohalogenation from halogenoethylene was studied with the fluoride ion in several solvents including CH_3CN, DMF, and n-butylcellosolve. It was found that crown accelerated the reaction in all cases but the effect appears to be quite dramatic in acetonitrile. Thus, from this study the fluoride ion was shown to be a potent base (Reaction 33).[158]

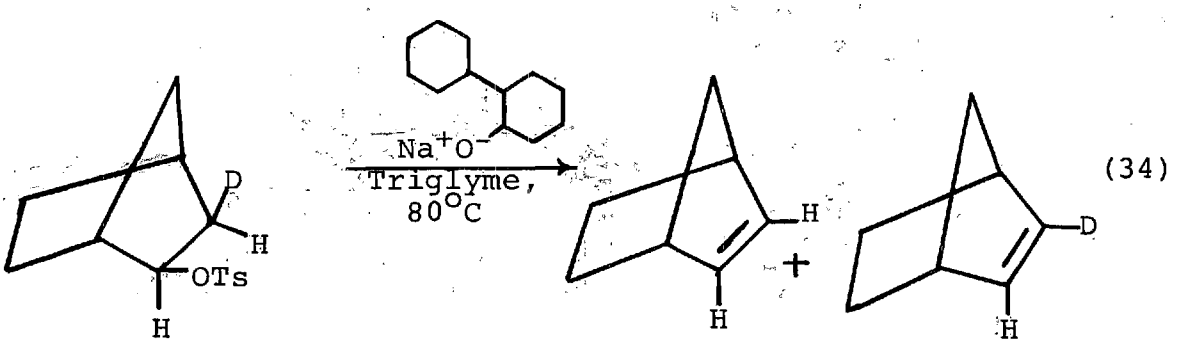


(33)

A more recent study by Henson[86] has shown the fluoride ion in 18-crown-6 acetonitrile solution ("naked" fluoride) to be a potent base, being especially useful in Michael type additions (Appendix 4).

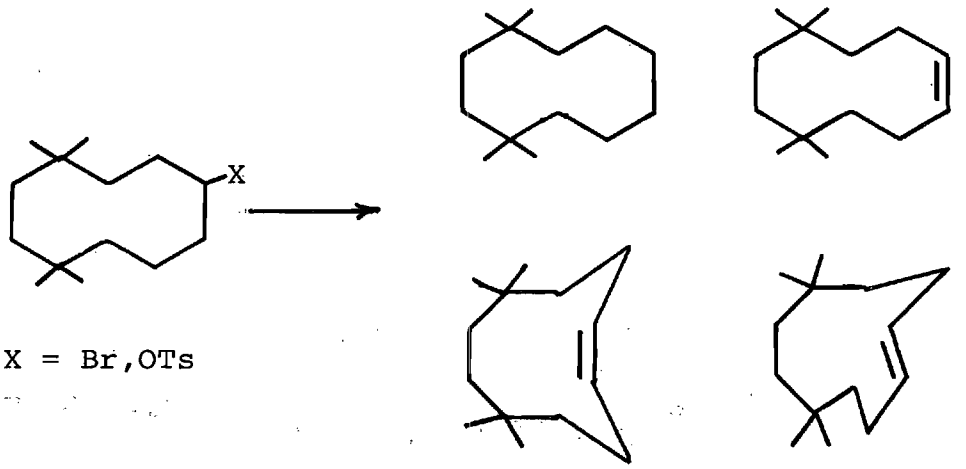
Reaction of exo-2-norbornyl-exo-3-d tosylate with the sodium salt of 2-cyclohexylcyclohexanol in triglyme produces norbornene containing no deuterium (Reaction 34). This represents an exclusive syn-elimination process. In the presence of 18-crown-6, however, 27% of the product contained

deuterium. Assuming an isotope effect of 6, the authors calculated a syn/anti rate ratio of 15:1 which contrasts sharply with a ratio of > 100:1 for associated base. These experiments demonstrate the effect of base association on syn- versus anti-elimination processes.[153] Base association effects have also been studied.[136] In each of the non-polar solvents studied, benzene and t-BuOH, syn-elimination is predominant whereas in the presence of crown the anti-elimination pathway predominates. In the more polar solvent DMF, the anti-elimination process dominates even in the absence of crown. In the presence of crown, however, the anti-pathway becomes even more pronounced (Reaction 35).



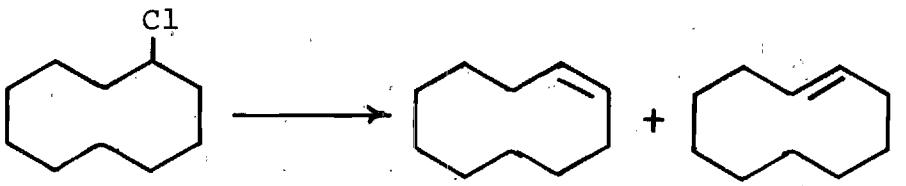
(34)

Elimination reactions on cyclodecyl chloride have been reported with a number of base-solvent systems (Reaction 36). The use of the t-BuOH-DMSO system resulted in anti-elimination predominantly whereas the use of lithium-cyclohexylamide in ethylether-hexane produced 13% anti-elimination product (this is increased to 32% in the presence



(35)

of tetramethyl-12-crown-4). The presence of dicyclohexyl-18-crown-6 with the KOtBu/t-BuOH system produces a small inverse effect. In general, however, it appears that base association facilitates syn-elimination processes.[159]



(36)

Concerning the stereospecificity and the regiospecificity of elimination reactions on organic substrates, it could thus be concluded that cis-product is favored with aggregated base while trans-product is favored in the presence of crown or in dipolar aprotic solvents.

CHAPTER II

EXPERIMENTAL

Instrumentation

All boiling points and melting points reported in this thesis are uncorrected and all temperatures are in degrees centigrade. Infrared spectra were obtained with a Perkin-Elmer Model 237B spectrophotometer (neat film for liquids or nujol mull for solids), and high-resolution infrared spectra were obtained with a Perkin-Elmer Model 621 spectrophotometer (nujol mull). The 1601.4 cm^{-1} absorption of polystyrene was used as a reference peak in all of the ir spectra (positional accuracy of ± 0.2 cm^{-1} for the high resolution ir). Proton nuclear magnetic resonance (nmr) spectra were obtained on either a Varian Model A60D or T60 spectrometer utilizing internal tetramethylsilane (TMS) as a standard. Mass spectra were obtained with either a Varian M66 or the Hitachi Perkin-Elmer RMU-7L instrument. Glpc work was conducted on a Varian Model 90P chromatograph equipped with a thermal conductivity detector and using helium carrier gas. All elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia. A Coleman Model-21 Flame Photometer was used to measure the solubilities of "naked" anions.

Chemicals

Acetonitrile and benzene (Fisher Certified A.C.S., reagent grade) as well as all extraction solvents and nmr solvents were used without further purification. Potassium fluoride (Allied Chemical, reagent grade), potassium acetate, and potassium chloride (Baker, reagent grade), potassium bromide and potassium iodide (Fisher Certified A.C.S., reagent grade), and potassium azide (highest purity, Vernon, Beverly, Massachusetts) used in the reactions involving 18-crown-6 were all dried at least 12 hours in an oven at 120° and finely powdered in a hot mortar before use. The powdered potassium salts were then stored in the oven at 120° at all times. Potassium cyanide (Fisher Certified A.C.S., reagent grade) was dried in a vacuum desiccator (1-2 mm, 105°, ca. 15 hours), placed in a flask, and tightly sealed so as to protect the salt against moisture uptake until needed.

Synthesis of 1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6), 1

Eighteen-crown-6, 1, was prepared by the method of Gokel and Cram and purified by the method of Liotta, Harris, and Cook.[14,15] A five-liter, three-necked flask equipped with a mechanical stirrer and water-cooled bearing, a reflux condenser, and a 500 ml dropping funnel was charged with 226 g (1.5 mole) of triethylene glycol (Matheson, Coleman, and Bell) in 1000 ml THF (Fisher). Potassium hydroxide (218 g, Fisher, 85% pellets) was dissolved in

120 ml distilled water and added in one portion to the stirred triethylene glycol mixture. After 30 minutes of stirring at ambient temperature the solution turned dark brown and considerable heat was evolved. A solution of 280 g (1.5 mole) of 1,8-dichloro-3,6-dioxaoctane (Eastman practical, 1.5 mole) in 200 ml THF was added from the dropping funnel in a thin stream to the stirred reaction mixture. The resulting mixture was then refluxed for 17 hours. The bulk of the solvent was removed by rotary evaporation (aspirator pressure), after which the rotary evaporator bath temperature raised to ca. 70°C to remove the bulk of the water present. The residual oil and solid was stirred with a mechanical stirrer for 30 minutes with one liter of methylene chloride, the salts removed by vacuum filtration, and the filtrate dried over $MgSO_4$. This solution was filtered and concentrated on a rotary evaporator and the residue distilled under vacuum. After an initial low-boiling forerun (bp 25-128°C at 0.2 mm) was carefully removed, two fractions boiling over a wide range were collected: (i) a main fraction (bp 129-140°C at 0.2mm) of relatively pure crown that crystallized on standing; and (ii) a dark-colored semi-solid fraction that consisted of relatively pure crown (bp 141-165°C at 0.2 mm). A total of 154.4 g (39%) of crude 18-crown-6 was obtained.

Each of the two fractions was purified separately by the acetonitrile complex. To 50 g of the semi-solid crude in a 250 ml Erlenmeyer flask was added 125 ml of acetonitrile (Fisher). The resulting slurry was heated until solution was effected. A magnetic stirring bar was added, and the top was equipped with a Drierite drying tube. As the solution slowly cooled to room temperature, vigorous agitation produced fine white crystals of the crown ether-acetonitrile complex. After reaching room temperature, the flask was cooled with stirring in an ice-acetone bath to complete precipitation. The mixture was quickly filtered under vacuum and the hygroscopic crystals were transferred to a 250 ml round-bottomed flask equipped with a magnetic stirrer, a vacuum take-off, and a heating mantle. The acetonitrile was removed over a period of two to three hours under 0.5 to 0.1 mm pump vacuum and low (ca. $\leq 40^{\circ}C$) heat. The pure, colorless crown ether (25 g, 50% yield) which crystallized on standing showed no ions above 265 in the mass spectrum and no significant hydroxyl absorption in the 3500 cm^{-1} region of the ir spectrum. The pure crown ether melted at $36-38^{\circ}$ (lit[16] mp $39-40^{\circ}$), showed only a sharp singlet at $\delta 3.53$ in the nmr (60 MHz, CCl_4, internal TMS), had ir absorption (neat) at 2875 (alkane C-H), 1450 and 1350 (alkane C-H), and 1120 cm^{-1} (ether C-O), and showed a mass spectrum having m/e 265 and 264 and abundant fragments at 89, 87, 59, 45, and 44.

Preparation of 2-Chloro-2-methylcyclohexanone, 34

Compound 34 was prepared by a standard procedure from the literature.[160] A 1000 ml, three-necked, round-bottomed flask equipped with a Teflon-coated stirring bar, a 500 ml pressure-equalizing dropping funnel and a gas outlet tube, was charged with a solution of 75 g (0.67 mole) of 2-methylcyclohexanone (Aldrich) in 340 ml reagent carbon tetrachloride (Fisher). A solution of 60 ml (0.70 mole) of sulfuryl chloride (Eastman practical) in 95 ml reagent carbon tetrachloride was added dropwise over a period of 4.0 hours to the stirred solution. After the addition was complete, stirring was continued for an additional 3 hours. The reaction mixture (light yellow solution) was then washed successively with three 100 ml portions of distilled water, three 100 ml portions of saturated sodium bicarbonate (until effervescence ceased), one 100 ml portion of saturated sodium chloride, and finally washed twice with 100 ml portions of distilled water. The organic phase was dried ($MgSO_4$), filtered under vacuum (aspirator suction), and the bulk of the solvent removed by rotary evaporation (aspirator pressure) at a bath temperature set at ca. 40°C. Distillation of the yellow crude product using water aspirator vacuum gave 84.0 g (85%, literature yield 83-85%) of colorless 2-chloro-2-methylcyclohexanone, bp 89-91° (23 mm) [lit[160] bp 94-96°C (27 mm)]. Infrared absorption (neat) at 1735 cm^{-1} (C=O);

nmr peaks (neat, internal TMS) at δ1.5 (3H singlet, methyl protons) and at δ3.6-1.6 (8H multiplet, ring protons).

Elimination Reactions Promoted by "Naked" Halides

Apparatus

The apparatus for the dehydrohalogenation reactions was the same in all cases. The reaction pot was a 50 ml round-bottomed flask equipped with a Teflon-coated stirring bar (1" x 3/8" needed to provide vigorous stirring to facilitate complete reaction), and a condenser topped by a drying tube (Drierite). Withdrawal of solution aliquots for analyses during the course of reaction was accomplished by stopping the stirring, quickly inserting an elongated pipette through the condenser into the flask, and withdrawing (suction bulb) the liquid. Stirring was continued as soon as possible to avoid "bumping" in the reflux systems. The withdrawn aliquots were placed in 1/2 dram vials, centrifuged to compact the salt present, and the liquid carefully pipetted off. The glc syringe utilized (Hamilton, 10 ml, gas tight) was rinsed thoroughly with water followed by acetone if long periods elapsed between injections in order to free the barrel of salt particles. For short time periods between tests, acetone washings were performed after each injection. After an injection was performed, the aliquot was returned to the reaction flask via a pipette through the condenser.

Attempted Preparation of 2-Methylcyclohexenone (2-Chloro-2-methylcyclohexanone-KI-Crown-Acetonitrile System), Method I

A 50 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 9.5 g (0.065 mole) of 2-chloro-2-methylcyclohexanone (2.2M), 20.0 ml of stock 0.30M 18-crown-6 in acetonitrile (0.0060 mole, 0.20M), and 19.92 g anhydrous potassium iodide (Fisher, 0.12 mole). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 80°C, 1-bromohexane as internal standard). After 21 hours, less than 5% of 2-methylcyclohexanone product was formed from 2-chloro-2-methylcyclohexanone which was present in ≥95% as shown by glpc analysis using an internal standard. The product 2-methylcyclohexenone was identified by comparison of its glpc retention time with a known sample.

Attempted Preparation of 2-Methylcyclohexenone (2-Chloro-2-methylcyclohexanone-KCl-Crown-Benzene System), Method II

A 50 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 9.5 g (0.065 mole) of 2-chloro-2-methylcyclohexanone (2.2M), 20.0 ml of stock (0.28M) 18-crown-6 in benzene (0.0056 mole, 0.19M), and 11.1 g (0.149 mole) of anhydrous potassium chloride (Baker). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 80°C, 1-bromohexane as internal standard). After 21 hours, only about 3% 2-methylcyclohexenone had been formed from

2-chloro-2-methylcyclohexanone which was present in about 97% as shown by glpc analysis using an internal standard. The product 2-methylcyclohexenone was identified by comparison of its glpc retention time with a known sample.

This same reaction, when carried out under somewhat similar conditions with acetonitrile solvent being used instead of benzene, gave 51% yield of product 2-methylcyclohexenone as reported by H. P. Harris.[182] In the absence of crown ether, only a few percent ($\leq$ 3%) of product was formed under the same conditions covering the same periods of time.

Preparation of 2-Methylcyclohexenone (2-Chloro-2-methylcyclohexanone-KBr-Crown-Acetonitrile System), Method III

A 50 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 9.5 g (0.065 mole) of 2-chloro-2-methylcyclohexanone (2.2M), 20.0 ml of stock (0.30M) 18-crown-6 in acetonitrile (0.0060 mole, 0.20M), and 17.33 g (0.149 mole) of anhydrous potassium bromide (Fisher). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 80^{o}C, 1-bromohexane as internal standard). After 6 hours, the starting material had completely disappeared and only one peak was present as shown by glc analysis. During the course of this reaction the solution turned from colorless to pink to red to red brown. The reaction mixture was

filtered under vacuum and the solid residue was washed with about 40 ml of hexane. The filtrate was analyzed by glpc using above internal standard and was found to contain 78% of 2-methylcyclohexenone.

The dark-brown filtrate was concentrated on a rotary evaporator and distilled under aspirator vacuum with a short-path distilling head to give 4.7 g (66%) 2-methylcyclohexenone (bp 77-79° at 27 mm) (Lit[156] bp 83-85°C at 35 mm); infrared absorption (neat) at 1673 cm^{-1} (conjugated C=O); nmr peaks (neat, internal TMS) at δ6.82 (1H multiplet, vinyl H), at δ2.1 (6H multiplet, aliphatic H), and at δ1.6 (3H singlet, $-CH_3$). The glpc retention time, infrared, and nmr spectra of this compound were identical with those of a known sample provided by H. P. Harris.[182]

Preparation of 2-Methylcyclohexenone (2-Chloro-2-methylcyclohexanone-KF-Crown-Acetonitrile System), Method IV

A 50 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 9.5 g (0.065 mole) of 2-chloro-2-methylcyclohexanone (2.2M), 20.0 ml of stock 0.3 M 18-crown-6 in acetonitrile (0.0060 mole, 0.20M), and 8.65 g (0.149 mole) of anhydrous potassium fluoride (Baker). The stirred solution was refluxed and monitored by glpc (3% SE 30, 5' x 1/4", 80°C, 1-bromohexane as internal standard). After 10 hours, the starting material had completely disappeared and only two peaks were present as shown by glc analysis of

the reaction mixture. Those two peaks were initially assigned as 2-methylcyclohexenone (56.4% by glc) and 2-fluoro-2-methylcyclohexanone (43.6% by glc). The assignments were based on glpc retention times which were identical with those of known samples provided by H. P. Harris.[182]

During the course of this reaction the solution turned from colorless to light green. The colored reaction mixture was filtered under vacuum (aspirator suction) and the solid residue was washed with about 20 ml of acetonitrile. The filtrate was analyzed by glpc using above internal standard and was found to contain 45% olefin and 32% 2-fluoro-2-methylcyclohexanone. The green filtrate was concentrated on a rotary evaporator and distilled under aspirator vacuum with a short-path distilling head to give a mixture of about equal amounts of two products (bp 67-78^{o}C at 27 mm). The compound eluted first from the glpc was assumed to be 2-fluoro-2-methylcyclohexanone based upon glpc comparison with a known compound while the compound eluted second was 2-methylcyclohexenone based upon glpc comparison of a known sample prepared earlier. No further attempt was made to separate these two compounds.

H. P. Harris[182] separated these two compounds by utilizing column chromatography with 150 g silica gel (Curtis, 100-200 mesh) in benzene (yielding a column 54 x 2.5 cm). In the absence of crown ether, only a few percent

(<5%) of the product compounds were formed under the same conditions covering the same periods of time.

Solubilities of "Naked" Anions in Solution

The different solubilities of KF, KCl, KBr, KI, KOAc, KN_3, KCN, and KSCN in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 were determined by measuring the concentration of potassium ion in each salt by flame photometry (Coleman Model-21).

Determination of Salt Concentrations in Solution

General

To determine the different concentrations of above potassium salts in solutions of 18-crown-6 in acetonitrile, the concentration of potassium ion was found by flame photometry. Standard solutions for the calibration curve for the Coleman Model-21 Flame Photometer were prepared in three 10.0 ml volumetric flasks[162a] by mixing 2.0 ml of stock 0.15M 18-crown-6 in acetonitrile, three different known weights of potassium salt, and enough distilled water to bring the total volume of each flask to the mark. A blank solution was also prepared in a 10.0 ml volumetric flask by diluting 2.0 ml of stock 0.15M crown-acetonitrile solution to the mark with distilled water. The flame photometer was adjusted to read zero scale divisions with the blank solution and 100 scale divisions with the standard

solution of highest concentration (ca. 1.0×10^{-3}M potassium salt). The two other solutions were then run and a plot of scale divisions versus concentration of potassium salt in solution was made.

A sample of potassium salt was solubilized by stirring excess anhydrous potassium salt at room temperature for 1.5 hours with the same stock solution of crown ether in acetonitrile that was used to prepare the standard solutions. This mixture was then centrifuged and exactly 2.0 ml of the clear supernatant liquid was carefully removed. This sample was diluted to the mark with distilled water in a 10.0 ml volumetric flask.

To determine the solubility of each potassium salt in acetonitrile without 18-crown-6, acetonitrile alone was stirred for 1.5 hours over excess anhydrous potassium salt. This mixture was likewise centrifuged and 2.0 ml of the clear supernant liquid was diluted with distilled water in a 10.0 ml volumetric flask.

The two unknown samples of each potassium salt in acetonitrile (with and without crown ether) were run on the flame photometer and the concentration of potassium ion in each was determined from the calibration curve.

Concentration of Potassium Bromide in Solution

Preparation of Stock 0.15M Crown-Acetonitrile Solution

A 50.0 ml volumetric flask was charged with 1.9822 g (0.075 mole) of 18-crown-6 and was then filled to the mark with acetonitrile (Fisher). The contents of the flask were shaken very well to dissolve completely the crown ether and give a homogeneous solution. The flask was then tightly stoppered and used subsequently in the following experiments.

Preparation of Stock 0.01M KBr-Water Solution

Anhydrous potassium bromide (0.2975 g, 0.0025 mole) was placed in a 250 ml volumetric flask which was then filled to the mark with distilled water. A homogeneous solution was then affected.

Preparation of Standard Solutions of Potassium Bromide

Standard solutions of potassium bromide (SS_1, SS_2, and SS_3) were prepared as follows:

SS_1 Twenty ml of 0.01M stock KBr-H_2O solution was diluted with 1.00 ml of 0.15M crown-acetonitrile solution and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 8.0×10^{-4}M KBr).

SS_2 Fifteen ml of 0.01M stock KBr-H_2O solution was diluted with 1.00 ml of 0.15M crown-acetonitrile solution and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 6.0×10^{-4}M KBr).

SS_3 Five ml of 0.01M stock KBr-H_2O solution was diluted with 1.00 ml of 0.15M crown-acetonitrile solution and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 2.0×10^{-4}M KBr).

Preparation of Blank

One ml of 0.15M crown-acetonitrile was diluted to the mark with distilled water in a 250 ml volumetric flask.

Preparation of Unknown Solution of KBr in 0.15M Crown-Acetonitrile

A sample of potassium bromide solubilized by 0.15M 18-crown-6 in acetonitrile was prepared by stirring excess anhydrous potassium bromide at room temperature for 1.5 hours with the same stock solution of crown ether in acetonitrile used to prepare the standard solutions. This mixture was then centrifuged and exactly 1.0 ml of the clear supernatant liquid was carefully removed. This sample was diluted to the mark with distilled water in a 250 ml volumetric flask.

Preparation of Unknown Solution of KBr in Acetonitrile (without Crown)

To determine the solubility of potassium bromide in acetonitrile without 18-crown-6, acetonitrile alone was stirred at room temperature for 1.5 hours over excess anhydrous potassium bromide. This mixture was likewise centrifuged and 1.0 ml of the clear supernatant liquid was diluted to the mark with distilled water in a 250 ml volumetric flask.

The concentration of K^+ (i.e., KBr) versus scale division readings (units from flame photometer) for each of the six different solutions prepared was measured. The

flame photometer was adjusted to read zero scale divisions with the blank solution (A 10.0 ml beaker was rinsed twice and filled with the blank solution. The beaker was then placed in the special slot in the photometer and the reading recorded.) and 100 scale divisions with the standard solution of highest concentration (ca. 8.0×10^{-4}M, standard solution A). The two other standard solutions were run and their readings in scale divisions recorded. A plot of scale divisions versus concentration of potassium bromide in solution was made. This linear plot was the calibration curve for the instrument. Finally, the two unknown samples of potassium bromode in acetonitrile (with and without crown ether) were run on the flame photometer and their respective readings in scale divisions recorded. The solution containing no crown ether registered about zero scale divisions just as the blank solution did. From the calibration curve, the solution containing 18-crown-6 contained 5.05×10^{-4}M potassium ion. The concentration of bromide in the original 0.15M crown-acetonitrile solution was calculated by multiplying 5.05×10^{-4} by 250, since 1.0 ml of the original solution was diluted to 250.0 ml with distilled water. This gave 1.25×10^{-1}M potassium bromide in 0.15M crown ether in acetonitrile at room temperature. In the absence of crown ether, the solubility of potassium bromide in acetonitrile at room temperature was likewise calculated and was found to be 2.04×10^{-3}M.

The following data (Table 1) was recorded for the concentration of potassium bromide when different solutions were run on the flame photometer.

Table 1. Solubility of KBr in Acetonitrile at 25°C in the Presence and in the Absence of 18-Crown-6.

Sample	First Reading (Scale Divisions)	Second Reading (Scale Divisions)	Corres. Conc. on Calibration Curve	Real Concentration of Salt
SS_1[a]	100.0	100.0	8.00×10^{-4} M	8.00×10^{-4} M
SS_2[a]	73.0	73.0	6.00×10^{-4} M	6.00×10^{-2} M
SS_3[a]	22.0	23.0	2.00×10^{-4} M	2.00×10^{-4} M
$W_{KBr/O}$[b]	62.5	62.0	5.05×10^{-4} M	1.25×10^{-1} M
W_{KBr}[c]	0.50	0.50	0.08×10^{-4} M	2.08×10^{-3} M
Blank	0.00	0.00	------	------

[a] SS_1, SS_2, and SS_3 are the three standard solutions 1, 2, and 3, respectively.
[b] $W_{KBr/O}$ is the unknown solution of potassium bromide in the presence of 0.15M crown ether-acetonitrile solution.
[c] W_{KBr} is the unknown solution of potassium bromide in acetonitrile alone.

Following this procedure, the different solubilities of KF, KCl, KBr, KI, KOAc, KCN, and KSCN in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 were determined by flame photometry (see Table 3).

In determining the concentration of some of the potassium salts reported in this thesis, the readings of some unknown samples when run on the flame photometer were out of scale (i.e., did not fit into the 0 to 100 scale divisions and thus did not fit into the different calibration curves) and the whole data had to be repeated diluting or concentrating the unknown solutions so as to fit into scale. In the case of potassium bromide, however, since the reading on the flame photometer of the unknown sample of potassium bromide in acetonitrile without crown ether registered about zero scale divisions just as the blank solution did, the experiment was repeated by preparing three standard solutions utilizing known concentrations of potassium bromide in acetonitrile alone, a blank solution and the same unknown solution of potassium bromide in acetonitrile alone prepared earlier. This time the solution of the unknown sample registered about 50 scale divisions. From the calibration curve, the solubility of potassium bromide in acetonitrile without 18-crown-6 was found to be 2.08×10^{-3} M.

An interesting experiment where a direct comparison of the solubilities of KI, KBr, KOAc, and KCN in acetonitrile without 18-crown-6 at room temperature could be obtained was the following: a stock solution of 0.01M KI-H_2O was prepared by adding 0.4150 g of anhydrous potassium iodide and distilled water to the mark of a 250 ml volumetric flask.

Standard solutions of potassium iodide (SB_1, SB_2, and SB_3) were prepared as such:

SB_1 Fifteen ml of 0.01M KI-H_2O was diluted with 20.0 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 6.0×10^{-4}M KI).

SB_2 Ten ml of 0.01M KI-H_2O was diluted with 20.0 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 4.0×10^{-4}M KI).

SB_3 Five ml of 0.01M KI-H_2O was diluted with 20.0 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask (resulting concentration: 2.0×10^{-4} M KI).

Blank Twenty ml of acetonitrile was diluted with distilled water to the mark of a 250 ml volumetric flask.

Preparation of Unknown Solutions of KI, KBr, KOAc, and KCN (W_{KI}, W_{KBr}, W_{KOAc}, and KCN, respectively)

W_{KI} One-half ml of clear supernatant was diluted with 19.5 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask.

W_{KBr} Fifteen ml of clear supernatant was diluted with 5.0 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask.

W_{KOAc} Twenty ml of clear supernatant was diluted with 0.01 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask.

W_{KCN} Twenty ml of clear supernatant was diluted with 0.01 ml acetonitrile and distilled water to the mark of a 250 ml volumetric flask.

The clear supernatants of the above potassium salts were prepared following the same standard procedure reported earlier in this thesis.

The flame photometer was adjusted to read zero scale divisions with the blank solution and 100 scale divisions

with the standard solution of highest concentration (ca. 6.0×10^{-4}M KI). The two other standard solutions were run and a plot of scale divisions versus concentration of potassium iodide in solution was made. This linear plot was the calibration curve for the instrument. The other unknown solutions of KI, KBr, KOAc, and KCN were run on the flame photometer and the concentration of potassium ion in each was determined (Table 2).

Table 2. Solubilities of KI, KBr, KOAc, and KCN in Acetonitrile at 25°C.

Sample	1st Reading from Photometer	2nd Reading from Photometer	Avg.	Conc. Shown on Calibration Scale	Real Concentration of Salt
SB_1	100.0	100.0	00.0	6.00×10^{-4}M	6.00×10^{-4}M
SB_2	68.0	67.4	67.7	4.00×10^{-4}M	4.00×10^{-4}M
SB_3	34.5	33.2	33.8	2.00×10^{-4}M	2.00×10^{-4}M
W_{KI}	36.2	36.4	36.3	2.12×10^{-4}M	1.06×10^{-1}M
W_{KBr}	21.2	21.4	21.3	1.25×10^{-4}M	2.08×10^{-3}M
W_{KCN}	16.0	15.8	15.9	0.95×10^{-4}M	1.19×10^{-3}M
W_{KOAc}	7.0	7.0	7.0	0.40×10^{-4}M	5.00×10^{-4}M
Blank	0.0	0.0	0.0	------	------

The same standard procedure reported earlier for obtaining the solubility of potassium bromide was utilized to

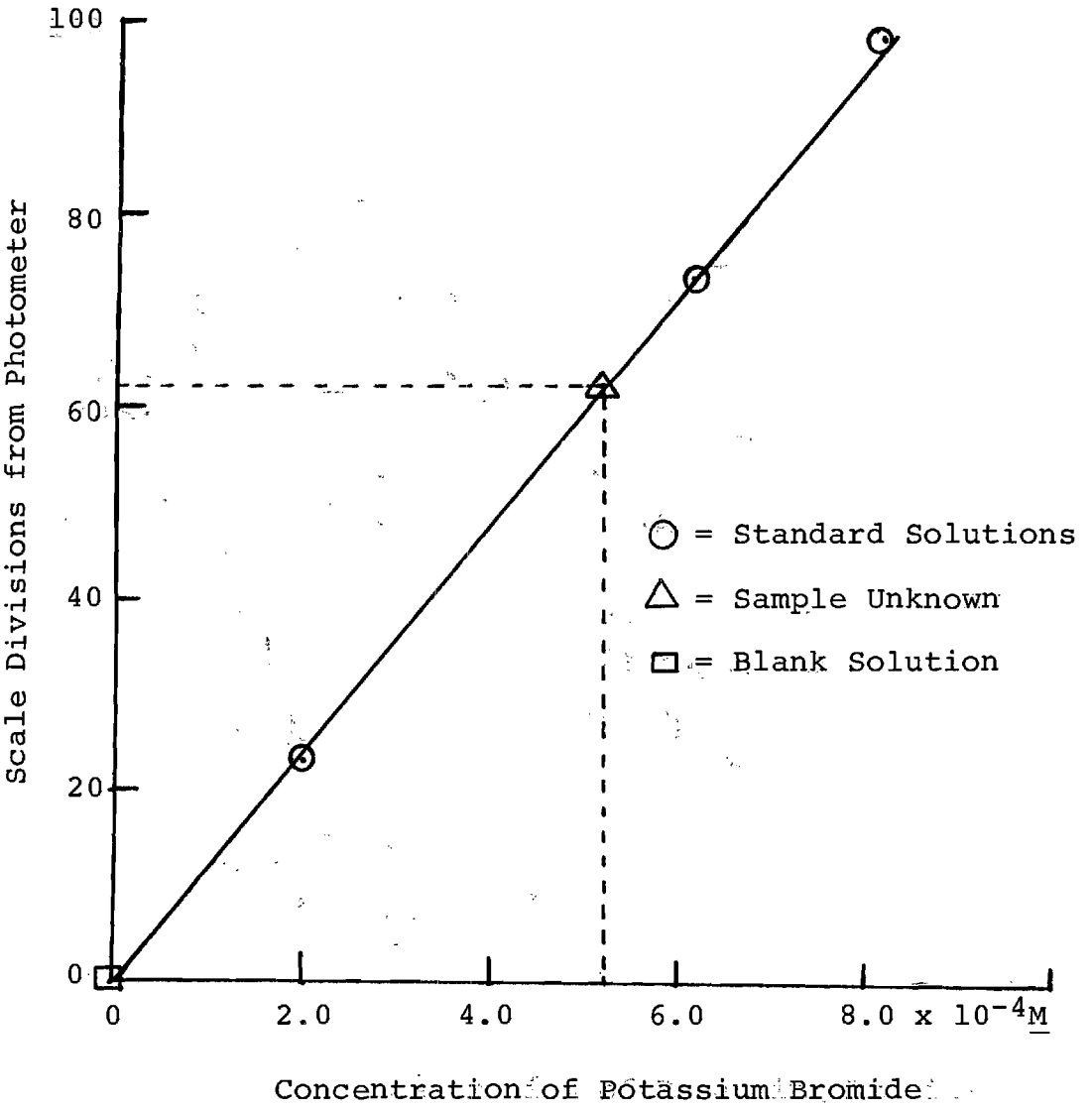


Figure 8. Plot of Scale Divisions Versus Concentration of Potassium Bromide in 0.15M 18-Crown-6-acetonitrile Solution at 25°C.

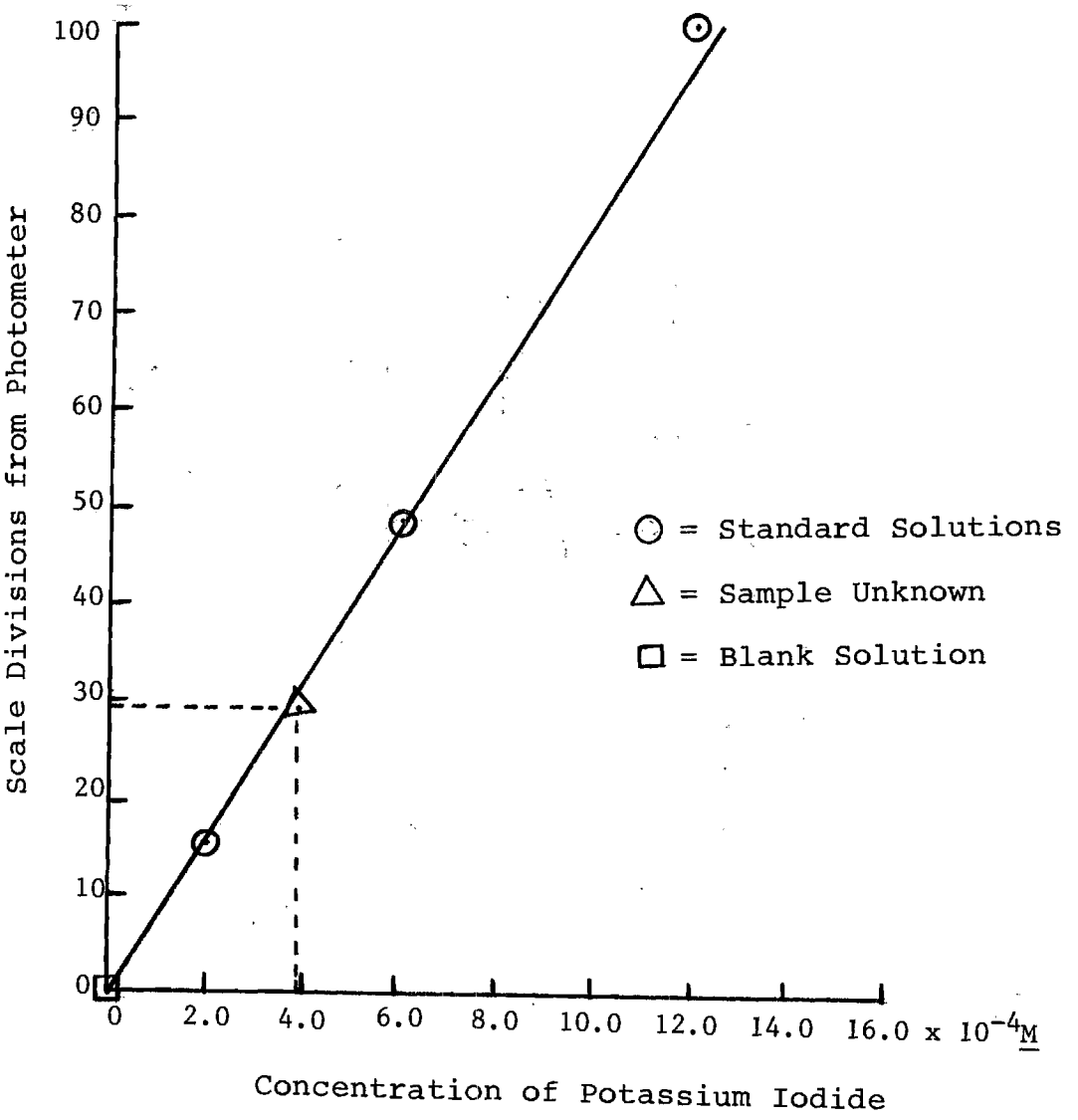


Figure 9. Plot of Scale Divisions Versus Concentration of Potassium Iodide in 0.15M 18-Crown-6-acetonitrile Solution at 25°C.

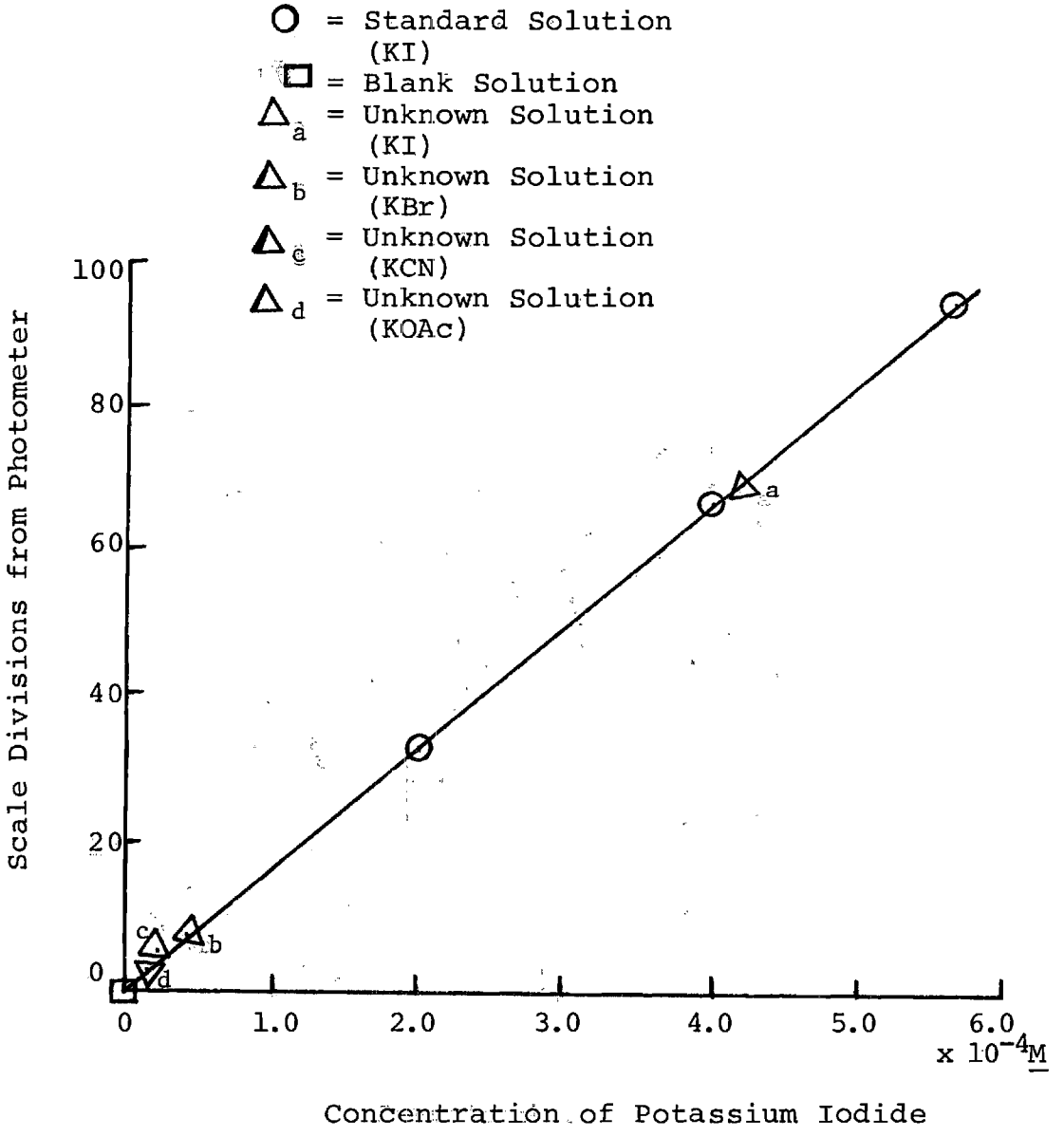


Figure 10. Plot of Scale Divisions Versus Concentration of Potassium Iodide in Acetonitrile at 25°C.

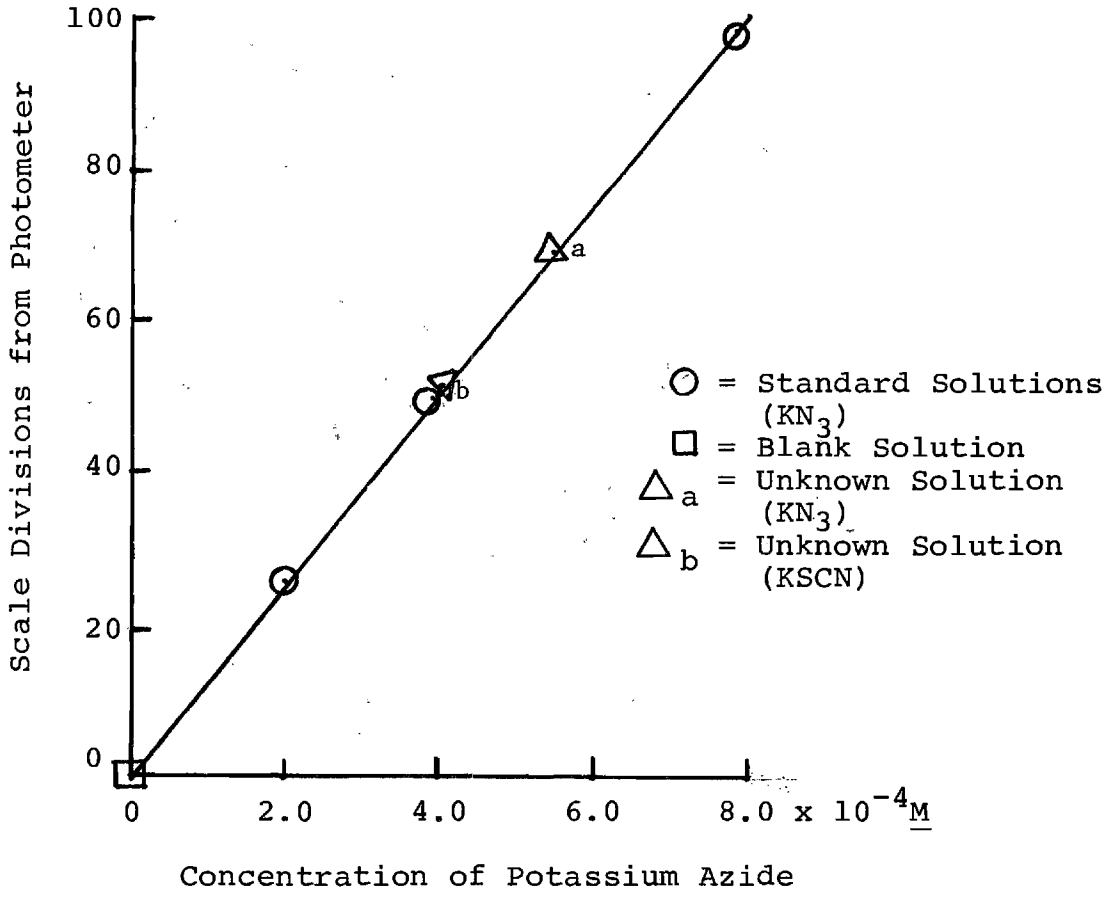


Figure 11. Plot of Scale Divisions Versus Concentration of Potassium Azide in 0.15M 18-Crown-6-acetonitrile at 25°C

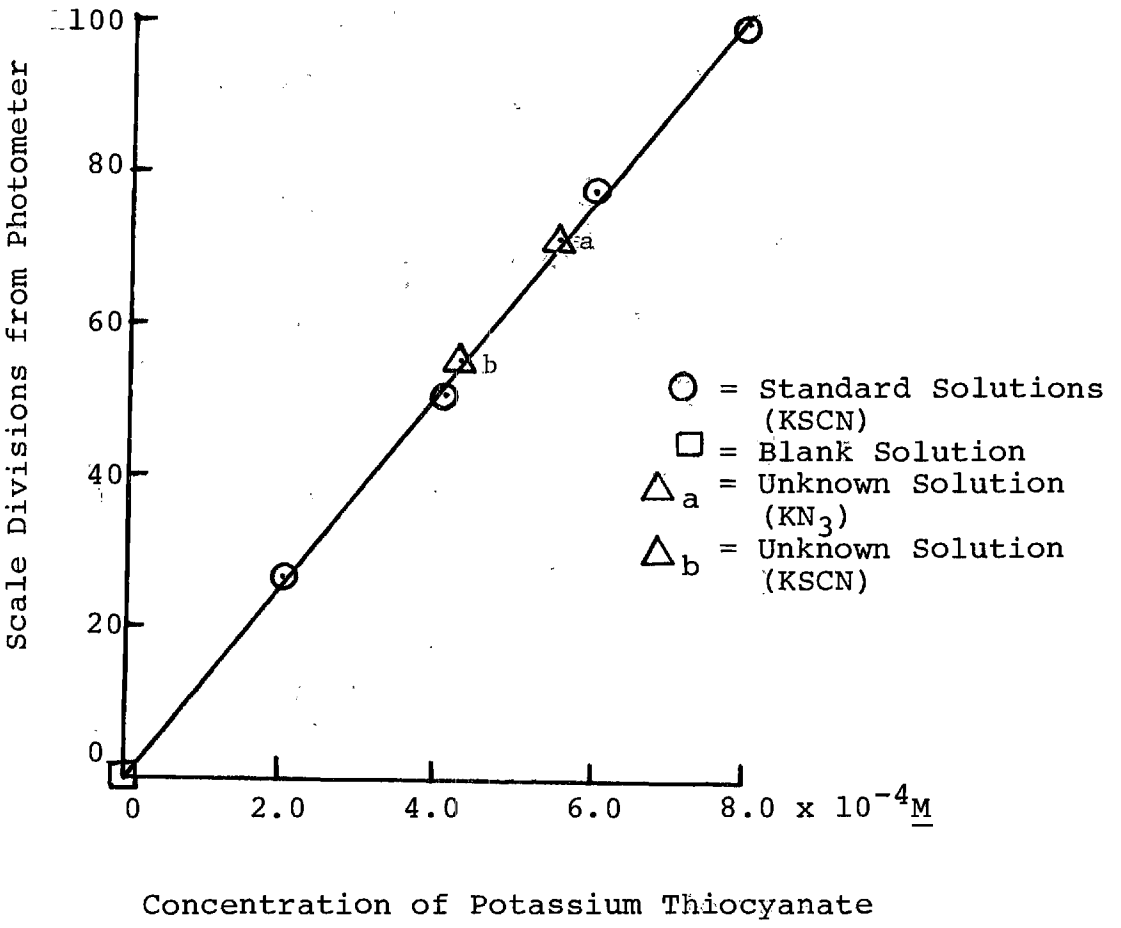


Figure 12. Plot of Scale Divisions Versus Concentration of Potassium Thiocyanate on 0.15M 18-Crown-6-acetonitrile at 25°C

obtain the solubilities of the other potassium salts. The solubility data obtained for the various salts KI, KBr, KCN, and KOAc double checks very well with the solubility data obtained for each salt alone. The other salts KN_3, KSCN, KF, and KCl were likewise treated and the solubility data obtained checked very well for each salt alone. It is important to note that the solubility data reported in this thesis was obtained by carefully repeating the experimentation on each salt twice (both in the presence and in the absence of 18-crown-6).

Displacement and Rearrangement Reactions Promoted by "Naked" Cyanide

Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Crown-Acetonitrile (Ambient) System], Method I

Into a 25 ml volumetric flask were placed 9.50 g (0.065 mole) of 2-chloro-2-methylcyclohexanone and the volume diluted to the mark with a 0.28M stock solution of 18-crown-6 [ca. 1.04 g (0.0042 mole)] in acetonitrile to give a final approximate solution concentration of 2.60M in reactant and 0.18M in crown.

A 100 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 10.62 g (0.163 mole) of dry powdered potassium cyanide. The prepared solution was poured directly over the salt, and the two-phase system was stirred vigorously at

ambient temperature. The course of the reaction was monitored by glc analysis [5% TCEPE (Tris-cyanoethyxypropane) 10' x 1/4", 151°C] which showed a $t_{\frac{1}{2}}$ of 17 minutes, a $t_{completion}$ of 35 minutes, and a yield of ca. 100% of 2-cyano-2-methylcyclohexanone. During the course of this reaction, the solution turned from colorless to light yellow. The reaction mixture was filtered (aspirator pressure) and the salts were washed with methylene chloride. The bulk of the solvent was removed by rotary evaporation (aspirator pressure) at ambient temperature.[163a] Five ml of water was added to the remains (water extracts any traces of KCN and preferentially dissolves crown. Moreover, addition of water should be conducted in the hood with caution.) and the heterogeneous solution was extracted twice with 15 ml portions of methylene chloride. The organic layer was dried ($MgSO_4$), concentrated on a rotary evaporator, and the residue distilled yielding 8.14 g (92.1%) of 2-cyano-2-methylcyclohexanone as a colorless liquid: bp 102-103°C at 23 mm (lit[163b-e] bp 94°C at 13 mm); nmr (neat, internal TMS), δ1.55 (3H singlet, $-CH_3$), δ2.0-0.8 (8H multiplet, ring protons) ppm; ir (neat, NaCl plates), 1725 (C=O) and 2240 (C≡N) cm^{-1}; and mass spectral peaks m/e 122, 109, 97, 94, 84, 78, 69, 68, 67, 55, and 54.

Elemental Analysis:

Calculated: for $C_8H_{11}NO$(35) C 70.04; H 8.08; N 10.21; O 11.66. Found: C 70.79; H 8.13; N 10.19; O 11.61.

Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Crown-Benzene (Ambient) System], Method II

Benzene solvent was utilized in this reaction instead of acetonitrile as reported in Method I. Into a 25 ml volumetric flask were placed 10.0 g (0.0683 mole) of 2-chloro-2-methylcyclohexanone and the volume was diluted to the mark with a 0.28M stock solution of 18-crown-6 [ca. 1.04 g (0.0042 mole)] in benzene to give a final approximate solution concentration of 2.73M in reactant and 0.18M in crown.

A 100 ml round-bottomed flask equipped with a magnetic stirrer and a reflux condenser with Drierite drying tube was charged with 10.79 g (0.166 mole) of dry, powdered potassium cyanide. The prepared solution was poured directly over the salt, and the two-phase system was stirred vigorously at ambient temperature. The course of the reaction was monitored by glc analysis (5% TCEPE, 10' x 1/4", 149°C), which showed a $t_{\frac{1}{2}}$ of 25 minutes, a $t_{completion}$ of 153 minutes, and a yield of ca. 100% of 2-cyano-2-methylcyclohexanone. The reaction product was worked up under exactly the same conditions as reported in Method I and the yield was 8.01 g (90.6%) of pure 2-cyano-2-methylcyclohexanone. The product was identified by comparison of its boiling point, nmr spectrum, and glpc retention time with those of the previously identified sample prepared by Method I.

Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Acetonitrile (Ambient) System], Method III

This reaction was carried out in the absence of crown ether. A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 8.5 g (0.058 mole) of 2-chloro-2-methylcyclohexanone and enough acetonitrile (Fisher) to make exactly 25.0 ml of 2.32M solution. To this was added 9.04 g (0.139 mole) of dry, powdered potassium cyanide. The mixture was stirred at ambient temperature and the course of the reaction was monitored by glc analysis (5% TCEPE, 10' x 1/4", 151°C), which showed a $t_{\frac{1}{2}}$ of 30 minutes, a $t_{completion}$ of 135 minutes, and a yield of ca. 100% of 2-cyano-2-methylcyclohexanone. The reaction product was worked up exactly as shown in Method I. Distillation of the final product yielded 8.06 g (91.2%) of 2-cyano-2-methylcyclohexanone. The product was identified by comparison of its boiling point, nmr spectrum, and glpc retention time with those of the previously identified sample.

Attempted Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Acetonitrile (Reflux) System], Method IV: Actually, Preparation of the "Favorskii Rearrangement Product", Method I

This reaction was carried out at reflux temperature and gave the "Favorskii rearrangement product" as the only product.

Into a 25 ml volumetric flask were placed 8.52 g (0.059 mole) of 2-chloro-2-methylcyclohexanone and the volume diluted to the mark with a 0.28M stock solution of 18-crown-6 [ca. 1.04 g (0.0042 mole)] in acetonitrile to give a final solution concentration of 2.33M in reactant and 0.17M in crown.

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 8.81 g (0.136 mole) of dry, powdered potassium cyanide. The prepared solution was poured directly over the salt, and the two-phase system was stirred vigorously at reflux temperature. The course of the reaction was monitored by glc analysis (5% TCEPE, 10' x 1/4", 150°C), which showed a $t_{\frac{1}{2}}$ of 16 hours and $t_{completion}$ of 80 hours. Furthermore, glpc analysis showed the presence of only one peak in the reaction product. That peak had a glpc retention time different from that of 2-cyano-2-methylcyclohexanone. During the course of this reaction the solution turned from colorless to light yellow to pink to red to red brown. The reaction mixture was filtered (aspirator pressure) and the salts were washed with three 4 ml portions of acetonitrile. The bulk of the solvent was removed by rotary evaporation (aspirator pressure) and the tarry residue was then distilled yielding 5.26 g (66%) of colorless "Favorskii rearrangement product"[164] identified as follows: bp 108-110°C

at 26 mm; nmr peaks ($CDCl_3$, external TMS) at δ1.52 (3H singlet, $-CH_3$), at δ3.1-7.5 (8H multiplet, ring protons); ir absorptions (neat, NaCl plates) at 1720 cm^{-1} (C=O) and 2220 cm^{-1} (conjugated-C≡N); and mass spectral peaks of 137 (M^+) and abundant fragments at m/e 122, 94, 82, 68, 67, and 55.

Elemental Analysis:

Calculated for $C_8H_{11}NO$ (36): C 70.04; H 8.08; N 10.21; O 11.66. Found: C 70.02; H 8.15; N 10.22; O 11.61.

The product has not been previously reported in the literature. This product is confirmed to be an isomer of 2-cyano-2-methylcyclohexanone as shown by mass spectral analysis and elemental analysis of the purified product. It is definitely not the 2-cyano-2-methylcyclohexanone because the two compounds give different glpc retention times, and different ir and nmr spectral data. Also, the compound is definitely not the 6-cyano-2-methylcyclohexanone isomer because this latter compound will exhibit a clear doublet at δ1.02 ppm for the methyl protons similar to the doublet exhibited by the methyl protons in 6-acetoxy-2-methylcyclohexanone but only a sharp singlet is exhibited for the methyl protons in the product identified here. Thus, based on spectral data as well as elemental analysis obtained for the unknown, it could be easily assigned as the "Favorskii rearrangement product", 36, which is also named 1-methylcyclopentanecarbonyl cyanide.

Attempted Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Crown-Acetonitrile (Ambient then Reflux) System], Method V

In a separate run which involved similar procedure (except for the work up) and exactly the same concentration of substrates as shown in Method I, the reaction was complete in 35 minutes and the reaction product was worked up in the following manner: the salts were filtered (aspirator suction), washed with acetonitrile and the filtrate reduced to ca. 1/3 volume by rotary evaporation (aspirator pressure). The residue was extracted with methylene chloride by a continuous extraction method for 24 hours. (This method was utilized earlier by Liotta, Cook, and Bowers[96] to remove traces of KCN from organic nitriles.) The extraction caused a change of color from light yellow to pink. The methylene chloride extract was then dried ($MgSO_4$), concentrated on a rotary evaporator and distilled under vacuum yielding 4.2 g (47.3%) of 2-cyano-2-methylcyclohexanone and 2.6 g (29.2%) of its isomer, the "Favorskii rearrangement product".

Attempted Preparation of 2-Cyano-2-methylcyclohexanone [2-Chloro-2-methylcyclohexanone-KCN-Crown-Acetonitrile-Acetone Cyanohydrin (Ambient then Reflux) System], Method VI

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 5.83 g (0.090 mole) of dry, powdered potassium cyanide. To this was added 0.819 g of 18-crown-6 (0.0031 mole, 0.21M), 9.0 ml of acetonitrile (Fisher), and 5.71 g

(0.039 mole) of 2-chloro-2-methylcyclohexanone (2.60M) in the order indicated. The two-phase system was stirred vigorously at ambient temperature. The course of the reaction was monitored by glc analysis (5% TCEPE, 10' x 1/4", 148°C). After 13 minutes, the reaction mixture was analyzed by glc analysis which showed the presence of ca. 60% of starting material, 2-chloro-2-methylcyclohexanone and ca. 40% of product, 2-cyano-2-methylcyclohexanone. At this stage 0.5 g (0.006 mole) of acetone cyanohydrin (Baker, 12.5 mole percent, 0.40M) was added to the reaction mixture. After stirring the reaction mixture at ambient temperature for 140 minutes, another 40% of the starting material was converted to product as evidenced by glc analysis which showed 20% of starting material and 80% of 2-cyano-2-methylcyclohexanone product. It was, therefore, concluded that acetone cyanohydrin does not divert the course of reaction to other products, especially 2-methylcyclohexanone, but it only retards the rate of the reaction.

At this stage, another 2.0 g (0.024 mole) of acetone cyanohydrin concentration (Baker) was added. That gave a total acetone cyanohydrin concentration of 0.030 mole, 42 mole percent, and 2.0M. After refluxing for 40 hours in the presence of acetone cyanohydrin only the displacement product, 2-cyano-2-methylcyclohexanone was formed as shown in the presence of only one peak corresponding to the above product which gave the same glpc retention time compared to

a known sample. Thus, it was concluded that after refluxing for 40 hours in the presence of acetone cyanohydrin, no rearrangement product was formed which would otherwise be smoothly effected in the absence of acetone cyanohydrin under the same conditions covering the same periods of time. When the same reaction mixture was refluxed further, however, a $t_{\frac{1}{2}}$ of 90 hours was reached. However, for converting 50% of the 2-cyano-2-methylcyclohexanone to its isomer, the "Favorskii rearrangement product" entered in. The reaction was stopped at this stage and was not studied any further.

Preparation of the "Favorskii Rearrangement Product" 36 [2-Cyano-2-methylcyclohexanone-KCN-Crown-Acetonitrile (Reflux) System], Method II

A 50 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and Drierite drying tube was charged with 4.5 g (0.033 mole) of 2-cyano-2-methylcyclohexanone (2.20M), 9.1 ml of stock 0.25M 18-crown-6 in acetonitrile (0.0023 mole, 0.16M), and 5.15 g (0.079 mole) of dry, powdered potassium cyanide. The two-phase system was stirred vigorously at reflux temperature and the course of the reaction was monitored by glc (5% TCEPE, 10' x 1/4", 130°C), which showed a $t_{\frac{1}{2}}$ of 2.0 hours, a $t_{completion}$ of 10 hours, and a yield of ca. 100% of the "Favorskii rearrangement product" 36. During the course of this reaction, the solution turned from colorless to pink. The reaction mixture was filtered (aspirator pressure) and the salts were

washed with two 10 ml portions of acetonitrile. The bulk of the solvent was removed by rotary evaporation and the organic residue distilled yielding 2.97 g (66.0%) of 1-methylcyclopentanecarbonylcyanide, the "Favorskii rearrangement product" of the starting material. This product was identified by comparison of its boiling point, nmr spectrum and glpc retention time with the previously identified sample. In the absence of crown ether, the reaction was refluxed for 55 hours, but no reaction was observed and only the starting material was recovered.

Preparation of the "Favorskii Rearrangement Product" 36 [2-Cyano-2-methylcyclohexanone-KCN-Crown-Benzene (Reflux) System], Method III

Benzene solvent was utilized in this reaction instead of the acetonitrile solvent utilized in the previous reaction (Method II). The same apparatus described earlier was charged with 4.70 g (0.034 mole) of 2-cyano-2-methylcyclohexanone (2.7M), 8 ml of a 0.27M stock solution of 18-crown-6 in acetonitrile (0.0021 mole, 0.17M), and 5.30 g (0.0816 mole) of dry, powdered potassium cyanide. The two-phase system was stirred vigorously at reflux temperature and the course of the reaction was monitored by glc (5% TCEPE, 10' x 1/4", 132°C), which showed a $t_{\frac{1}{2}}$ of 3 hours and a $t_{completion}$ of 31 hours. During the course of the reaction the solution turned from colorless to pink to dark brown. The reaction mixture was worked up exactly the same way described earlier.

The yield was 2.2 g (47.3%) of the "Favorskii rearrangement product". The product was identified by comparison of its boiling point, nmr spectrum and glpc retention time with the previously identified sample. In a similar experiment, but in the absence of crown ether, less than 5% of the reactant was converted to products.

Attempted Preparation of the "Favorskii Rearrangement Product" 36 [2-Cyano-2-methylcyclohexanone-Crown-Acetonitrile (Reflux) System], Method IV

This reaction was carried out in the absence of KCN in order to help study the mechanism of the rearrangement reaction.

A 50 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 4.16 g (0.0284 mole) of 2-cyano-2-methylcyclohexanone (2.37M) and 7.6 ml of 0.28M stock solution of 18-crown-6 in acetonitrile (0.0021 mole, 0.18M). The homogeneous solution was stirred vigorously at reflux temperature. After 50 hours no rearrangement product was observed and only the starting material was recovered.

Attempted Preparation of the "Favorskii Rearrangement Product" 36 [2-Cyano-2-methylcyclohexanone-KCN-Crown-Acetonitrile-Acetone Cyanohydrin (Reflux) System], Method IV

A 50 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 4.9 g (0.034 mole) of 2-cyano-2-methylcyclohexanone (2.43M), 8.0 ml of 0.33M stock 18-crown-6-acetonitrile solution (0.0026 mole, 0.19M) and 1.0 g (6.012 mole)

of acetone cyanohydrin (Baker, 0.86M), 5.08 g (0.078 mole) of dry, powdered potassium cyanide were then added and the two-phase system was vigorously stirred at reflux temperature. The progress of the reaction was followed by glc analysis (5% TCEPE, 10' x 1/4", 130°C) which showed a $t_{\frac{1}{2}}$ of 7 hours, and at completion of 30 hours. During the course of the reaction, the reaction mixture turned from colorless to pink to red brown. The reaction product was worked up following the same procedure reported earlier. Three grams (62.3%) of the "Favorskii rearrangement product" were obtained. The product had identical nmr spectra, boiling point, and glpc retention time to that of a known sample.

Preparation of 4-Methylcyclohexanone[165]

The chromic acid oxidizing reagent (Jones reagent)[166] was first prepared by dissolving 67 g (0.67 mole) of chromium trioxide (Fisher) in 125 ml of distilled water in a 500 ml Erlenmeyer flask. Fifty-eight ml of concentrated sulfuric acid (sp.gr. 1.84, 106.7 g, 1.09 mole) was added and the mixture stirred vigorously. The flask became hot and the precipitated salt was dissolved by addition of minimum quantity (85 ml) of distilled water. Finally, the flask was cooled to 5-10° for about 10 minutes.

A solution of 57.0 g (0.50 mole) of 4-methylcyclohexanol (Aldrich, 99% pure mixture of cis- and trans-isomers) in 900 ml of reagent grade acetone (Aldrich) was cooled to 10°C in a two liter three-necked flask immersed in an ice

bath and equipped with an efficient mechanical stirrer with a water-cooled bearing, a thermometer, and a pressure-equalizing dropping funnel. The cooled oxidizing reagent solution (125 ml) was added dropwise with stirring at such a rate as to maintain the temperature of the reaction mixture at about 15-20°C. Addition was continued until the orange color of the oxidation solution persisted for about 20 minutes. Sodium bisulfite (Fisher, 10.0 g, 0.096 mole) was added in small portions until the brown color of the chromic acid had disappeared from the upper layer of the two-phase mixture. The upper layer was decanted and the dense, green, lower layer was extracted twice with 100 ml portions of petroleum ether. Sodium bicarbonate (Fisher, 25.0 g, 0.29 mole) was added in small portions and with caution to the collective organic extracts and the suspension was stirred vigorously until the PH of the resulting solution tested neutral. The whole suspension was transferred into a two liter separatory funnel, 300 ml of water was added, the suspension stirred vigorously, and the lower layer decanted. The upper organic layer was washed successively with two 100 ml portions of saturated sodium chloride, three 100 ml portions of saturated sodium bicarbonate, and one 100 ml portion of water. The organic layer left after these washings was dried ($MgSO_4$), filtered under vacuum, and the bulk of the solvent removed by rotary evaporation (aspirator pressure). Distillation of the remaining residue under

reduced pressure gave 46.8 g (82.1%) of colorless 4-methylcyclohexanone, bp 54°C at 11 mm (lit[165] bp 169-170.5°C at 750 mm); infrared absorption (neat) at 1715 cm^{-1} (C=O) with no OH band observed in the 3500 cm^{-1} region; nmr (neat, internal TMS), δ0.75 (3H doublet, $-CH_3$), and δ1.0-2.44 (8H multiplet, ring protons).

Attempted Preparation of 2-Chloro-4-methylcyclohexanone[167]

A 500 ml three-necked flask equipped with a magnetic stirrer, a dropping funnel, and a gas outlet tube was charged with a solution of 10.55 g (0.094 mole) of 4-methylcyclohexanone in 65 ml of reagent grade carbon tetrachloride (Fisher). A solution of 20.1 ml (0.234 mole) of sulfuryl chloride in 25 ml of reagent grade carbon tetrachloride (Fisher) was added dropwise. The course of the reaction was monitored by glc analysis (5% TCEPE, 10' x 1/4", 110°C) which showed the disappearance of the starting material and the appearance of three new peaks for the products. These peaks were shown later to be 2-chloro-4-methylcyclohexanone (53%), 2,6-dichloro-4-methylcyclohexanone (37%), and 2,2-dichloro-4-methylcyclohexanone (10%). The contents of the flask were transferred into a 250 ml separatory funnel and were washed successively with four 50 ml portions of saturated sodium bicarbonate, twice with 50 ml portions of saturated sodium chloride, and twice with 50 ml portions of water. The collective aqueous layer was extracted with 100 ml of carbon

tetrachloride. This extract added to the original organic layer was dried ($MgSO_4$), filtered under vacuum, and the bulk of the solvent removed by rotary evaporation. Distillation under reduced pressure gave a fraction (2.2 g, 14.0%) bp 78-86°C at 4 mm (lit[167] bp of cis- and trans-mixture 85-100°C at 11 mm); nmr (neat, internal TMS); δ0.9 ppm (3H doublet, $-CH_3$); and δ4.8-4.4 (8H doublet of doublets, ring protons); ir (neat) at 1715 cm^{-1} (C=O).

Elemental Analysis:

Calculated for $C_7H_{11}ClO$: C 57.33; H 7.52; Cl 24.23; O 10.92. Found: C 57.51; H 7.45; Cl 24.21; O 10.83.

A second fraction (2.8 g; bp 85-93°C at 9 mm) exhibited three peaks by glc analysis and was assumed to be a mixture of mono- and di-chloro compounds and was not investigated further. A third fraction (2.4 g; bp 92-105°C at 9 mm) exhibited nmr peaks (neat, internal TMS) at δ1.0 ppm (3H doublet, $-CH_3$) and at δ4.8-3.2 (7H multiplet, ring protons); ir (neat) at 1720 cm^{-1} (C=O).

Elemental Analysis:

Calculated for $C_7H_{10}Cl_2O$: C 46.46; H 5.52; Cl 38.67; O 9.41. Found: C 46.15; H 5.63; Cl 38.85; O 9.37.

This latter data clearly proved the identity of the dichloro-compound. Also, the glc analysis of this fraction showed one peak only corresponding to the 2,6-dichloro-4-methylcyclohexanone (the 2,2-dichloro-4-methylcyclohexanone

rearranges to the more thermodynamically stable isomer, the 2,6-dichloro-ketone in the presence of an acid which is true in the present case). Thus, this attempted procedure to prepare the mono-chloro-ketone was not very successful since the mono-chloro-ketone was isolated in poor yield (14.0%).

In a separate run, distillation of the products under atmospheric pressure left a brown, viscous, polymeric material.

Preparation of 2-Chloro-4-methylcyclohexanone[168]

To the middle neck of a 500 ml three-necked flask, equipped with a magnetic stirrer, was affixed a gas inlet tube. The diffusion head of the tube reached almost to the bottom of the flask and helped diffuse incoming chlorine gas evenly and smoothly. The gas inlet tube in turn was connected from the outside via a T-joint to nitrogen gas and chlorine gas simultaneously. The stream of nitrogen gas sweeping through the reaction mixture assisted in carrying the chlorine gas along and helped in keeping the pressure from dropping in the reaction flask and consequently prevented the pump oil from being sucked into the reaction flask. A 250 ml filter flask which also served as a trap for pump oil was connected simultaneously to the reaction flask and to another trap that dipped seven inches into pump oil and had an inlet and outlet tube.

The reaction flask was charged with 40 g (0.36 mole) of 4-methylcyclohexanone (Aldrich) and 150 ml of water.

The solution was stirred vigorously and 28.9 g (0.40 mole) of chlorine gas (Matheson, 15.0 ml) was bubbled in (the gas was allowed to leave a five-pound cylinder and condense into a test tube, previously marked to 15 ml and cooled with a dry ice-acetone bath in a 400 ml beaker). The test tube was periodically removed from the ice bath and the gas was bubbled as rapidly as it was absorbed (10-15 minutes).

The heavier chlorocyclohexanone layer was separated and combined with three 75 ml ether extracts of the aqueous phase. The collective organic extracts were then washed successively with a 75 ml portion of water and a 100 ml portion of saturated sodium chloride solution. The organic layer was dried ($MgSO_4$), filtered under vacuum, and the bulk of the solvent removed on a rotary evaporator. Distillation of the residue utilizing a spinning band column with distilling head gave 7.8 g (19.5%) of recovered starting material, 20.2 g (38.3%) of 2-chloro-4-methylcyclohexanone (12.5 g of which consisted of the pure cis-isomer and 8.5 g consisted of cis- and trans-isomers in the ratio of 1:1.4 of cis- to trans-isomers as shown by glc analysis of the pure isolated products) and 22.3 g (33.4%) of 2,6-dichloro-4-methylcyclohexanone.[169] These products were identified by comparison of their boiling points, nmr spectra and glpc retention times with those of known samples.

Preparation of Cis-2-cyano-4-methylcyclohexanone[164]

Into a 25 ml volumetric flask were placed 18.0 g (0.123 mole) of 2-chloro-4-methylcyclohexanone (>95% cis-isomer) and enough 0.30M stock solution of 18-crown-6 [1.59 g (0.006o mole)] in acetonitrile to give a final solution concentration of 3.51M in reactant and 0.17M in crown.

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 21.6 g (0.334 mole) of dry, powdered potassium cyanide. The prepared solution was poured directly over the salt and the two-phase system was stirred vigorously at ambient temperature. The course of the reaction was monitored by glc analysis (3% SE 30, 5' x 1/4", 103°C) which showed a $t_{\frac{1}{2}}$ of 3.1 hours, a $t_{completion}$ of 7.0 hours, and a yield of ca. 100% of 2-cyano-4-methylcyclohexanone. During the course of this reaction, the solution turned from colorless to light brown. The reaction mixture was filtered (aspirator pressure) and the salts were washed with small portions of methylene chloride (Fisher, 25 ml). The bulk of the solvent was removed by rotary evaporation at ambient temperature. Twenty ml of methylene chloride (solvent grade) and 10 ml of water were added to the remaining residue in a 100 ml separatory funnel. The organic layer was dried ($MgSO_4$) and the bulk of the solvent removed by rotary evaporation.

Distillation of the final residue yielded 12.2 g (73%) of colorless cis-2-cyano-4-methylcyclohexanone bp 75-80°C at

2.1-1.5 mm; infrared (neat) at 1720 cm^{-1} (C=O) and 1740 cm^{-1} (C≡N, not conjugated); nmr (neat, internal TMS) δ0.9 ppm (3H doublet, $-CH_3$) and δ4.2-3.6 (8H multiplet, ring protons) with an overall spacing of 18.2 cps, showing proton on the same carbon with the cyano group to be axially oriented.

Elemental Analysis:

Calculated for $C_8H_{11}NO$: C 70.07; H 8.03; N 10.21; O 11.60. Found: C 70.17; H 8.07; N 10.25; O 11.51.

Less than 5% reaction occurred in the absence of crown ether under the same conditions covering the same period of time.

Preparation of Cis-2-acetoxy-4-methylcyclohexanone

A 100 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 6.38 g (0.069 mole) of dry, powdered potassium acetate, 4.93 g (0.033 mole) of 2-chloro-4-methylcyclohexanone (ca. a ratio of 1.4 of cis- to trans-isomer) and 7.0 ml of 0.27M stock solution of 18-crown-6 [ca. 0.50 g (0.00189 mole)] in acetonitrile to give a final solution concentration of 2.76M in reactant and 0.16M in crown.

The two-phase system was stirred vigorously at reflux temperature and the course of the reaction was monitored by glc (3% SE 30, 5' x 1/4", 103°C) analysis which showed a $t_{1/2}$ of 2.4 hours, a $t_{completion}$ of 7.0 hours, and the appearance of three new peaks (ca. 96% cis-2-acetoxy-4-methylcyclohexanone, 2% trans-2-acetoxy-4-methylcyclohexanone and, 2%

4-methylcyclohexenone). During the course of this reaction, the solution turned from colorless to faint yellow. The reaction mixture was filtered under vacuum and the salts were washed with small portions of methylene chloride (Fisher, 25 ml). The filtrate was concentrated on a rotary evaporator and distilled under reduced pressure to give 4.60 g (82%) of cis-2-acetoxy-4-methylcyclohexanone; bp 75-85°C at 0.34 mm (lit[170] bp 53-55°C at 0.15 mm); infrared absorption (neat) at 1740 cm^{-1} (ester C=O) and 1720 cm^{-1} (C=O); nmr peaks (neat, internal TMS) at δ1.94 (3H singlet, CH_3CO-), at 0.92 (3H coublet, $-CH_3$), at δ2.66-1.12 (7H multiplet, ring protons), and at 5.02-3.60 (1H doublet of doublets, J=6-9 cps, showing proton on the same carbon with acetate group to be axially oriented); and mass spectrum m/e 170 (M^+) and abundant fragments at 128, 81, and 43.

In the absence of crown ether, less than 5% reaction occurred under the same conditions covering the same period of time.

Addition Reactions Performed with "Naked" Cyanide and Acetone Cyanohydrin: Hydrocyanation of Δ^4-Cholesten-3-one

General

The apparatus for the hydrocyanation reactions was the same in all cases. The reaction pot was a 50 ml round-bottomed flask equipped with a Teflon-coated stirring bar (1" x 3/4" needed to provide vigorous stirring to facilitate

complete reaction), a condenser topped by a drying tube (Drierite). Withdrawal of solution aliquots for analysis during the course of hydrocyanation reactions was accomplished by stopping the stirring bar, quickly inserting an elongated pipette through the condenser into the flask, and then withdrawing (suction bulb) the liquid. Stirring was continued as soon as possible to avoid "bumping" in the reflux systems. The withdrawn aliquots were placed in 1/2 dram vials, centrifuged to compact the salt present, and the liquid carefully pipetted off the solid. Nmr spectra of the aliquot samples were obtained on either a Varian Model A60D or T60 spectrometer utilizing external TMS as a standard. After nmr analyses were performed, the aliquot samples were not returned to the reaction pot. That was done mainly to avoid interrupting the anhydrous state of the reaction and also to avoid erroneous computation of $t_{completion}$ of the reaction since the time elapsed in obtaining the nmr spectra of the aliquot samples would be hard to account for. When a reaction yield was required no aliquot samples were removed, and, in general the reaction was usually stopped one hour after it had been completed as shown from a previously monitored run. In general, the reaction was complete when the nmr analysis (CH_3CN, external TMS) of the crude reaction mixture showed no remaining olefin proton signals in the 4-6 ppm region.

Preparation of 5α- and 5β-Cyanocholestanone, Method I

Into a 10 ml volumetric flask were placed 0.56 g (0.0015 mole) of Δ^4-cholesten-3-one, and the volume was raised to the mark with a 0.21M stock solution of 18-crown-6 [0.76 g (0.0020 mole)] in benzene. The crown-reactant solution was combined with 0.26 g (0.0030 mole) of acetone cyanohydrin (Baker) to give a final approximate solution concentration of 0.14M in substrate, 0.19M in crown, and 0.29M in acetone cyanohydrin.

A 25 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 0.2 g (0.0029 mole) of dry, powdered potassium cyanide (Fisher). The prepared solution was poured directly over the salt, and the two-phase system was stirred vigorously at ambient temperature. The course of the reaction was followed by nmr techniques by observing the disappearance of vinyl proton signals in the 4-6 ppm region [after ca. 15 hours, nmr analysis (benzene, external TMS) of the aliquot sample showed no remaining olefin proton bands at 5.55 ppm During the course of this reaction, the solution turned from colorless to yellow red. The reaction mixture was filtered under vacuum and the solid residue was washed with ca. 5 ml of benzene. Eight ml of water was added to the filtrate (water extracts traces of KCN and preferentially dissolves crown). The aqueous layer was separated and extracted with 10 ml of methylene chloride. The combined organic extracts

were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. On evaporation of the solvents, the crystalline crown-cyano (5 α- and 5 β-) cholestanone complexes fell out of solution. Three ml of benzene (Fisher) was added to the solid-liquid mixture and the complex was dissolved with the application of hot air from the heat gun (ca. 2 minutes). The 5 α- and 5 β-isomers were separated from each other by column chromatography (30 g Alumina, acid-washed, Brockman activity II). Elution with petroleum ether-benzene (4:1) gave 50 mg (10%) of crude 5 α-isomer, mp 175-178°C (lit[171,172] mp 181-183°C). Recrystallization of this fraction from ethanol afforded 39 mg (7%) of the 5α-isomer, mp 178-181°C. Further elution with petroleum ether-benzene (2:1 and 1:1) afforded 481 mg (73%) of crude 5 β-isomer, mp 118-122°C (lit[171,172] mp 126-128°C). Recrystallization of this fraction from ethanol afforded 395 mg (70%) of the 5 β-isomer, mp 122-124°C. High resolution infrared spectra with a Perkin-Elmer Model 621 spectrophotometer (nujol mull) exhibited absorptions at 2238 cm^{-1} (C≡N) and at 1702 cm^{-1} for the 5 α-isomer. Furthermore, nmr spectra (benzene, internal TMS) of the 5 α-isomer coupled with a fraction collected from another run gave a peak for the methyl protons (at C_9) at 1.13 ppm while the nmr spectra (benzene, internal TMS) of the 5 β-isomer gave a peak for the methyl protons (at C_9) at 1.28 ppm. That these are different peaks was shown by the nmr analysis

of a mixture of 5 α- and 5 β-isomers which exhibited two different peaks at 1.13 ppm and 1.28 ppm attributed to the 5 α- and the 5 β-isomers, respectively.

Moreover, ORD (optical rotary dispersion) curves for the separate isomers compared favorably with those reported by Nagata et al.[173] for the respective isomers. In addition, elemental analyses of the pure isolated isomers compared very well with the calculated theoretical values.

Keeping the same concentrations of substrates as reported above (Run 2, Table 7) but using one stoichiometric amount of KCN instead of two, the reaction was ca. 80% complete after stirring at ambient temperature for 30 hours. In Run 3, Table 7, using conditions similar to those reported in Run 2, Table 7, except that the reaction was carried at 52°C, the reaction was complete in 10 hours and showed a ratio of 1:4.2 of 5α:5β-cyano isomers. Moreover, with one equivalent KCN but under reflux temperature (keeping other conditions similar to those reported in Runs 2 and 3, Table 7), the reaction was complete in 3 hours and showed a ratio of 1:3.2 of 5α:5β-cyano isomers. With catalytic KCN and at reflux temperature (Run 5, Table 7), the reaction was complete in 5 hours and showed a ratio of 1:4.0 of 5α:5β-cyano compounds. In all cases (Runs 2, 3, 4, and 5, Table 7), good isolated yields of individual isomers were obtained (83-86%) and no cyanide hydrolysis product (amides or lactams) or dimers could be detected. If present, these products would

have eluted (from the column chromatography used) after the 5 α-cyano isomer but before the β-isomer which elutes last. But none of these side products were observed by carefully separating the cyano products by column chromatography.

The absence of each of crown ether, KCN, or acetone cyanohydrin was enough to prevent the reaction from occurring. For example, in the absence of KCN but the presence of crown ether and acetone cyanohydrin, no reaction occurred after stirring at reflux temperature for 33 hours (Run 11, Table 7). In the absence of acetone cyanohydrin but the presence of crown ether and KCN, no reaction occurred after stirring at reflux temperature for 31 hours (Run 12, Table 7). Moreover, in the absence of crown ether but the presence of KCN and acetone cyanohydrin, no reaction occurred after stirring at reflux temperature for 32 hours (Run 1, Table 7).

Preparation of 5α - and 5β -Cyanocholestanone, Method II

Acetonitrile solvent was utilized in this method (Runs 6, 7, 8, 9, and 10, Table 7) instead of benzene solvent utilized in the previous method (Runs 1, 2, 3, 4, 5, 11, and 12, Table 7). In Run 7, Table 7, the most successful reaction carried out under the conditions of Method II, exactly the same concentration of crown ether, substrate, and acetone cyanohydrin were utilized except that one equivalent amount of KCN was used and the reaction was carried out at reflux temperature as compared to two equivalent amounts of KCN and ambient conditions for the reaction temperature as utilized

in Run 2, Table 7. Progress of reaction was followed by nmr techniques by observing the disappearance of vinyl proton signals in the 4-6 ppm region [after ca. 5 hours, nmr analysis (CH_3CN, external TMS) of an aliquot sample showed no remaining olefin proton band at 5.55 ppm]. During the course of this reaction, the solution turned from colorless to red brown. The reaction mixture was filtered under vacuum and the solid residue was washed with ca. 6 ml of benzene; 6 ml of water was added to the filtrate followed by 15 ml of benzene (Fisher). The aqueous layer was separated and extracted with 10 ml of benzene. The combined organic extracts were treated exactly as reported in Method I. There was isolated 95 mg (15.4%) of the 5α-cyano isomer in pure form along with 378 mg (60.6%) of the 5β-cyano isomer.

IR, nmr, ord, mp, and elemental analysis of each of the 5α- and the 5β-isomers obtained in this run compared very well with those obtained in previous methods as well as with those reported in the literature.

Different variations of this method were utilized and most of them were not as successful as reported in Method I. Thus, no reaction occurred at ambient temperature after stirring for 40 hours compared to complete reaction in Method I (Run 2, Table 7). With catalytic amounts of KCN, 50% reaction occurred after refluxing for 10 hours. Also, the absence of each of crown ether, KCN, or acetone cyanohydrin was found to prevent the reaction from occuring. Excellent isolated

yields of hydrocyanation products were obtained in acetonitrile (84-86%, Runs 7 and 8, Table 7) and no cyanide hydrolysis products (amides or lactams) or dimers could be detected. The reaction appears to proceed more rapidly in benzene than in acetonitrile (Runs 3 and 9, Runs 4 and 7, Table 7). This last observation is attributed to the greater solubility of cholestenone in benzene as compared to acetonitrile (cholestenone is extremely soluble in benzene at room temperature, while hardly soluble in acetonitrile). This is why the reaction with acetonitrile proceeds only at reflux temperatures (compare Runs 8 and 9, Table 7).

In Run 5, Table 7, the hydrocyanation reaction was carried out using catalytic amounts of KCN and ca. one half the amount of crown ether as utilized in other runs. The reaction product in this case was worked up slightly differently. The crude reaction product was concentrated by rotary evaporation (aspirator pressure) to ca. half volume and the remaining solution (containing KCN, crown, cyano products, benzene, and other complexes present in solution) was added to a previously prepared column chromatography. The 5α - and 5β -cyano compounds were eluted and separated as previously reported.

Attempted Preparation of 5α - and 5β - Cyanocholestanone, Method III

The hydrocyanation of Δ^4-cholesten-3-one was attempted using silver cyanide (instead of potassium cyanide) along with crown ether and acetone cyanohydrin.

Silver cyanide was prepared as follows: into a 500 ml round-bottomed flask equipped with a Teflon-coated stirring bar (2" x 5/8") and a 500 ml pressure equalizing dropping funnel was added a solution of 85 g (0.5 mole) of silver nitrate (Fisher) in 300 ml of distilled water. KCN (32.5 g, 0.5 mole, Fisher) dissolved in 100 ml of distilled water was added dropwise with vigorous stirring. AgCN precipitation started to form with the first drop of KCN-H_2O solution (during the addition, lights were turned off because AgCN is photosensitive). After the addition was complete AgCN (white gray precipitate) was collected by suction filtration. Water was pulled off under reduced pressure (0.1 mm) for 30 hours. Nmr analysis of an aliquot sample (taken from a solution of 5.0 AgCN in 6 ml benzene) showed the absence of OH bands from water (which usually shows at 5.2 ppm).

Into a 10 ml volumetric flask were placed 0.50 g (0.0013 mole) of Δ^4-cholesten-3-one, and the volume was raised to the mark with a 0.19M stock solution of 18-crown-6 0.48 g (0.0018 mole) in benzene. The crown-reactant solution was combined with 0.24 g (0.0028 mole) of acetone cyanohydrin (Baker) to give a final approximate solution

concentration of 0.13M in substrate, 0.17M in crown and 0.27M in acetone cyanohydrin.

A 25 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charges with 0.35 g (0.0026 mole) of dry silver cyanide. The prepared solution was poured directly over the salt, and the two-phase system was stirred vigorously at ambient temperature. The course of the reaction was followed by nmr analysis following the disappearance of vinyl protons in the 4-6 ppm region. After 23 hours, less than 10% reaction occurred as shown by the presence of vinyl protons at 5.55 ppm.

The same solution in the flask was then refluxed with stirring for 20 hours and nmr analysis showed that less than ca. 30% reaction had occurred. The reaction was stopped and was not worked any further being incompatible with the hydrocyanation methods I and II reported earlier in this thesis.

Attempted Preparation of 5α- and 5β-Cyanocholestanone, Method IV

The hydrocyanation of Δ^4-cholesten-3-one was also attempted utilizing quaternary ammonium salts as catalysts in place of crown ethers.

To each of four 25 ml round-bottomed flasks equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was added 0.40 g (0.0014 mole, 0.14M) of Δ^4-cholesten-3-one, 0.58 g (0.0018 mole) of tetra-n-butylammonium bromide (Fisher, 0.18M) or 0.48 g (0.0014 mole) of

benzyltriethylammonium chloride (Eastman, 0.14M) or 0.33 g (0.0014 mole) of cetyltrimethylammonium bromide (Ashland, 0.14M) or 0.60 g (0.0014 mole) of N-tallow pentamethylpropane diammonium dichloride (Ashland, 0.14M), 9.6 ml of benzene (Fisher), 0.15 g (0.0017 mole) of acetone cyanohydrin (Baker, 0.17M), and finally 0.20 g (0.0029 mole) of dry, powdered potassium cyanide (Fisher). The four different reactions were allowed to stir at ambient temperature at the same time and the extent of the reactions was measured by nmr analysis (aliquot samples were analyzed every four hours). After 25 hours, the first three reactions proceeded very slowly as shown by the faint yellow color developed in the reaction flasks and as shown by nmr analysis. Heating was then applied and the reactions were stirred under reflux temperatures for 22 hours and nmr analysis showed the presence of vinyl protons at 5.55 ppm indicating that the reactions were not complete (estimated 25-40%). The reactions were then stopped and were not studied any further.

The fourth reaction, i.e., that carried out with N-tallowpentamethylpropanediammoniumdichloride catalyst, looked very promising. During the course of the reaction, the color of the solution turned yellow then brown red in ca. 5 hours.

After stirring at ambient temperature for 19 hours, the reaction was complete as shown by nmr analysis. Being extremely miscible in water, efforts were made to extract the

quaternary diammonium dichloride salt with water, but it was noticed that as soon as 10 ml of water were added to the benzene solution (from this last reaction in a 250 ml separatory funnel), a milky emulsion immediately formed. Application of hot air from the heat gun followed by addition of a 6 ml saturated solution of sodium chloride did not help break the emulsion and/or help separate layers. The contents of the separatory funnel were then transferred into a 500 ml separatory funnel and 50 ml of methylene chloride was added, but the emulsion persisted. Finally 200 ml of petroleum ether and 20 ml of water were added, the contents of the separatory funnel were shaken very well and the aqueous layer was extracted first with 200 ml benzene and then with 200 ml CH_2Cl_2. The collective organic layers were dried ($MgSO_4$), filtered, and the solvents evaporated on a rotary evaporator leaving a yellow oily product that was left to dry in a 50 ml round-bottomed flask equipped with a Drierite drying tube. Nmr analysis ($CDCl_3$, external TMS) of the crude reaction product showed the presence of complex multiplets corresponding to long alkyl chains from the quaternary salt which overlapped with the bands from the methyl protons that usually show in the 1.1 to 1.35 ppm region. The nmr analysis did fail to show any vinyl proton bands in the 4-6 ppm region.

Preparation of the Octalones 71 and 72

A slightly modified procedure for the preparation of 67 and 68 as given in Organic Chemistry Experiments,[174-177] Part III, Chemistry 3383 was utilized (Figure 17).

A 500 ml round-bottomed flask equipped with a magnetic stirring bar and fitted with a Dean-Stark trap and a reflux condenser was charged with 49.0 g (0.50 mole) of cyclohexanone 65 (Aldrich), 50.0 g of pyrrolidone (0.72 mole) (Fisher), and 0.95 g (0.0056 mole) of p-toluenesulfonic acid in 150 ml of benzene (Fisher). The solution was refluxed with stirring for 2.25 hours until ca. 12 ml of water were separated. The solution was refluxed for an additional 15 minutes to insure complete reaction. The reaction mixture was cooled to ambient temperature and the bulk of the benzene and excess pyrrolidone were removed by rotary evaporation. Distillation of the yellow residual liquid under reduced pressure afforded 66.7 g (88.3%) of colorless 1-(1-cyclohexenyl)pyrrolidone, enamine 66, bp 67-69°C at 1.0 mm.

A 1000 ml three-necked flask equipped with a reflux condenser with a Drierite drying tube, a thermometer, a magnetic stirring bar, and a 250 ml dropping funnel was charged with 350 ml of reagent grade benzene (Fisher) and 66.5 g (0.43 mole) of enamine 66. To that solution was added, dropwise and with stirring over 60 minutes, 32.5 g (0.46 mole) of methyl vinyl ketone (Fisher). During the exothermic reaction the temperature of the reaction mixture was

kept at 25-30°C by cooling with an external ice-water bath. After the addition was complete, the mixture was refluxed with stirring for ca. 18 hours. The reaction mixture was then cooled and treated with a buffer solution prepared from 25 ml of acetic acid, 25 ml of water, and 12.5 g of sodium acetate. The resulting mixture was refluxed with stirring for 4 hours and then cooled. The aqueous layer was separated and extracted with 100 ml of benzene. The combined benzene solutions were washed successively with 100 ml of aqueous (10%) HCl, 100 ml of saturated $NaHCO_3$, and 50 ml of saturated aqueous NaCl. The organic layer was dried ($MgSO_4$), filtered, and the bulk of the solvent removed by rotary evaporation. The yellow brown residual liquid was distilled under reduced pressure to give a fraction (1) 12.0 g (18.7%), bp 25-82°C (0.6 mm) and another fraction (2), 47.1 g (73.6%), bp 82-84°C (0.6 mm). Glc analysis (3% SE 30, 5' x 1/4", 130°C) of the fractions showed fraction (2) to consist of ca. 97% of 71 and ca. 3% of 72, while the first fraction consisted of ca. 83% of 71 and ca. 17% of 72.

No attempt was undertaken to separate the isomers of fraction (2) since the unconjugated isomer 72 would not be hydrocyanated and would stay unchanged in the reaction flask.

Hydrocyanation of $\Delta^{4(10)}$-Octalin-3-one 71

The hydrocyanation of 71 was attempted using "naked" cyanide-acetone cyanohydrin. The hydrocyanation reaction was

carried out under three different sets of conditions as shown in the following systems.

(1) 71-"Naked" Cyanide-Acetone Cyanohydrin-Acetonitrile (Reflux Temperature) System.

Into a 10 ml volumetric flask were placed 1.0 g (0.0067 mole) of 71 (a mixture of 97% of 71 and 3% of $\Delta^{9(10)}$-octalin-3-one 72), and the volume was raised to the mark with a 0.15M stock solution of 18-crown-6 [ca. 0.33 g (0.00126 mole)] in acetonitrile. The crown-reactant solution was combined with 0.68 g (0.0080 mole) of acetone cyanohydrin (Baker) to give a final approximate concentration of 0.67M in substrate, 0.13M in crown and 0.80M in acetone cyanohydrin.

A 25 ml round-bottomed flask equipped with a magnetic stirrer, reflux condenser and Drierite drying tube was charged with 0.45 g (0.0067 mole) of dry, powdered potassium cyanide (Fisher). The prepared solution was poured directly over the salt and the two-phase system was stirred vigorously at reflux temperature. Progress of the reaction was followed by glc analysis (30% SE 30, 5' x 1/4", 135°C). After 15 minutes, glc analysis showed the disappearance of ca. 85% of the starting substrate 71 ($t_{retention}$, 3 minutes) and the appearance of a new peak for the products ($t_{retention}$, 4.5 minutes). During the course of the reaction, the solution turned from colorless to red brown in 10 minutes. The reaction was stopped after 90 minutes and glc analysis showed the conversion of about 95% of 71 into products. Utilizing

a different column (20% Carbowax on Chromasorb W, equipped with a thermal conductivity detector and a helium flow rate of 45 ml/minute, temperature was set at 100°C and was programmed to increase 10°C/minute until the temperature reached 200°C). Two peaks were observed for the products (in the ratio of 3:7). It is believed that these two coalesced peaks correspond to the cis- and trans-cyanooctalones 73 and 74, respectively. These two peaks could not be resolved by a variety of different columns. Nagata[173] has reported the glpc analysis of 73 and 74 using a Shimazu gas chromatograph Model GC-1C equipped with a thermal conductivity detector. Under these conditions the two peaks were separated using a 3% QF-1 on Chromosorb W (3 m x 3 mm stainless steel column) at 160° with a nitrogen flow rate of 200 ml/minute with retention times of cis- and trans-cyanooctalones 73 and 74 found to be 16.5 minutes and 18.0 minutes, respectively.

(2) 71-"Naked" Cyanide-Acetone Cyanohydrin-Benzene (Ambient Temperature) System

In a separate run benzene solvent was utilized instead of acetonitrile and the reaction was carried out at ambient temperature. All other conditions reported in system (1) were left the same (i.e., the same concentration of substrates, procedures, etc.). After stirring for 3 hours at ambient temperature, glc analysis of the crude reaction product showed the disappearance of ca. 95% of the starting substrate and

the appearance of a new peak which had the same retention time as previously reported in system (1). Glc analysis of this product on 20% Carbowax on Chromosorb W column [see (1)] showed two peaks, poorly resolved, in the ratio of ca. 1:9. It is believed that these two peaks correspond to cis- and trans-cyanooctalones 73 and 74, respectively. These peaks could not be resolved any further using a variety of different columns under varying glc conditions.

(3) 71-"Naked" Cyanide-Acetone cyanohydrin-Acetonitrile (Ambient Temperature) System

This reaction was effected under the same conditions reported in system (1) except that the reaction was carried out at ambient temperature instead of at reflux temperature as in (1). This reaction was done for comparison purposes, i.e., mainly to see whether or not it would succeed faster in benzene solvent than in acetonitrile (as was found in the hydrocyanation reaction with cholestenone 66). After stirring at ambient temperature for 10 hours, only ca. 70% of the starting substrate 71 had reacted, and, compared to system (2), where greater than 95% conversion to products was observed in three hours under the same conditions, one can easily conclude that the reaction went much faster in benzene than in acetonitrile solvent. The reaction in system (3) was allowed to go to 80% completion, but was not studied any further.

Hydrocyanation of 9-Methyl- $\Delta^{4(10)}$-Octalin-3-one[178] 75

The hydrocyanation of 75 was attempted utilizing "naked" cyanide-acetone cyanohydrin.

Into a 10 ml volumetric flask were placed 1.0 g (0.0061 mole) of 75 and the volume was raised to the mark with a 0.15M stock solution of 18-crown-6 [ca. 0.33 g (0.0013 mole)] in benzene. The crown-reactant solution was combined with 0.60 g (0.0071 mole) of acetone cyanohydrin (Baker) to give a final approximate solution concentration of 0.61M in substrate, 0.13M in crown, and 0.71M in acetone cyanohydrin.

A 25 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser with Drierite drying tube was charged with 0.40 g (0.0061 mole) of dry, powdered potassium cyanide (Fisher). The prepared solution was poured directly over the salt and the two-phase system was stirred vigorously at ambient temperature. The reaction was followed by glc analysis (3% SE 30, 5' x 1/4", 135°C). After 15 hours, glc analysis showed about 85% of the starting substrate 75 to have been converted to products. Glc analysis of products using 20% Carbowax on Chromosorb W column [see (1)] , showed two peaks, poorly resolved, in the ratio of ca. 1:4. It is belived that these two peaks correspond to trans- and cis-cyano ketones 76 and 77, respectively. Nagata[173] reported retention times of 16.0 and 11.5 minutes, for the trans- and

cis-isomers 76 and 77, respectively, on 3% PEG-6000 on Chromosorb W (3 m x 3 mm stainless steel column) at 170° with a nitrogen flow rate of 50 ml/minute. No further work was attempted in that regard.

Displacement and Elimination Reactions: Reactions of Potassium Cyanide and Potassium Acetate with Organic Substrates under Liquid-Liquid Phase-Transfer Catalytic (Heterogeneous) Conditions

Apparatus

The apparatus for the potassium cyanide and potassium acetate reactions was the same in all cases. The reaction pot was a 100 ml round-bottomed flask equipped with a Teflon-coated stirring bar (1" x 3/8" needed to facilitate complete reaction), a West condenser with no Drierite drying tube required since the reactions were carried out in the presence of aqueous salt solutions. Withdrawal of solution aliquots for analyses during the course of reaction was accomplished by halting the stirring bar, quickly inserting an elongated pipette through the condenser into the flask, and then withdrawing (suction bulb) the liquid. Stirring was continued as soon as possible to avoid "bumping" in the reflux systems. The withdrawn aliquots were dried (anhydrous magnesium sulfate, 5 minutes) in 1/2 dram vials, centrifuged to compact the salt present, and the liquid carefully pipetted off the solid. The glc syringe utilized (Hamilton, 10 ml, gas-tight) was rinsed thoroughly after use with water followed by acetone to free the barrel of any salt particles. After injection was performed, the remaining liquid was returned (through the condenser) to the reaction flask *via* a pipette.

infrared (neat, NaCl plates), 2925 cm^{-1} (alkane C-H), 2240 cm^{-1} (C≡N), 1457 cm^{-1} (CH_2), and 1375 cm^{-1} (CH_3); and mass spectral peaks at m/e 139 and abundant fragments at 97, 83, 55, 43, and 41. By glpc and nmr, no olefinic products could be detected.

In the absence of 18-crown-6 (Run 5, Table 8), less than 5% reaction occurred under the same conditions covering the same period of time.

When the reaction was carried out with the potassium cyanide completely dissolved in water (Run 3, Table 8), glc analysis (3% SE 30, 5' x 1/4", 118°C) showed a $t_{\frac{1}{2}}$ of 9.5 hours, a $t_{completion}$ of 39.2 hours, and a yield of ca. 100% of 1-cyanooctane. The reaction mixture was worked up exactly as reported in Run 1, Table 8. Distillation of the crude reaction product gave 4.9 g (89.9%) of pure 1-cyanooctane identified by comparison of its nmr spectra and glpc retention time with those of the previously identified sample of 1-cyanooctane.

1-Cyanooctane, Method II

The procedure was as in Method I, except that 5.35 g (0.0281 mole) of 1-bromooctane (Aldrich, 99%, 13.70 mole percent) was substituted for 1-chlorooctane. 18-Crown-6 (0.44 g, 0.0016 mole, 0.82 mole percent) and 1.5 ml water (0.083 mole, 40.60 mole percent) to give a final solution concentration of 3.82M in reactant and 0.28M in crown. Monitoring of the

course of reaction (Run 2, Table 8) by glc analysis (3% SE 30, 5' x 1/4", 118°C) showed a $t_{\frac{1}{2}}$ of 0.6 hours, a $t_{completion}$ of 0.75 hours, and a yield of ca.100% of 1-cyanooctane. The reaction was worked up exactly as reported in Run 1, Table 8. Distillation of the crude product gave 3.6 g (93.2%) of colorless 1-cyanooctane identified by comparison of its glpc retention time with that of a known sample. When the reaction was carried out in the absence of 18-crown-6 (Run 6, Table 8), less than 5% reaction occurred after refluxing for 172 hours.

When potassium cyanide was completely dissolved in water (Run 4, Table 8), the reaction was complete after 2.2 hours. Five grams (91.5%) of colorless 1-cyanooctane was obtained and identified with a known sample by its nmr spectra and glpc retention time.

2-Cyanooctane,[179,180] Method I

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 21.4 g (0.1111 mole) of 2-bromooctane (Aldrich, 99%, 15.34 mole percent, 4.77M), 2.2 g 18-crown-6 (0.0083 mole, 1.10 mole percent). To this was added 21.7 g (0.3338 mole) of powdered potassium cyanide (Fisher) and the two-phase system was stirred vigorously at reflux temperature (Run 8, Table 8; pot temperature was 117°C). The course of the reaction was monitored by glc analysis (3% SE 30, 5' x 1/4", 87°C) which showed a $t_{\frac{1}{2}}$ of

4.17 hours, a t_{end} of 8.0 hours, and two product peaks: one at $t_{retention}$ of 6.0 minutes (8% due to octenes) and the other at $t_{retention}$ of 5.4 minutes (92% due to 2-cyanooctane). The $t_{retention}$ of 2-bromooctane was 4.4 minutes. Nmr analysis (CH_3CN, external TMS) showed the disappearance of the $CH_3C\underline{H}(Br)CH_2$ peak at δ5.28, the appearance of the $CH_3C\underline{H}(CN)CH_2$ peak (δ2.47), and the appearance and area growth of a complicated multiplet (δ5.15 ppm, olefin proton region).

The pink reaction mixture was filtered (aspirator suction) and the salt remaining on the filter paper was washed with 10 ml portions of methylene chloride. Fifty ml of distilled water was added and the aqueous solution was extracted with four 75 ml aliquots of methylene chloride. The combined extracts were dried ($MgSO_4$), filtered (aspirator suction), and the bulk of the solvent removed by rotary evaporation at low heat (ca. 30°C). Distillation gave 0.7 g (4.1%) of a fraction (olefinic products), bp 21-50°C at 22 mm and 13.3 g (86.2%) of a second fraction (2-cyanooctane), bp 60-61°C at 1.5 mm (lit[179-180] bp 55°C at 1.0 mm). The low-temperature chromatogram (3% SE 30, 5' x 1/4", 35°C) overlapped in appearance and $t_{retention}$ with that of an isolated and characterized mixture of 1-octene and cis-, trans-2-octene (supplied by H. P. Harris).[182]

The 2-cyanooctane product exhibited ir absorption (neat) at 2930 (alkane C-H), 2240 (C≡N, unconjugated), 1460 (CH_2),

1375 (CH_3), and 1325 (CH) cm^{-1}; nmr (neat, internal TMS), at δ2.30 (1H multiplet, $CH_3\underline{C}H(CN)CH_2$) δ1.50 (10H multiplet, internal $-CH_2$), δ1.15 [3H doublet, $\underline{C}H_3CH(CN)$], and δ1.07 (3H triplet, $-CH_2\underline{C}H_3$); and mass spectral peaks at m/e 138 (parent ion -1H, 4%) and abundant fragments at 124, 110, 96, 83, 69, 55, and 43.

In the absence of 18-crown-6 (Run 12, Table 8), less than 5% reaction occurred under the same conditions covering the same period of time.

When the reaction was carried out with the potassium cyanide completely dissolved in water (Run 10, Table 8), glc analysis (3% SE 30, 5' x 1/4", 90°C) showed a $t_{\frac{1}{2}}$ of 8.0 hours and a $t_{completion}$ of 17.1 hours.

2-Cyanooctane, Method II

The procedure was as in Method I, except that 20.0 g (0.134 mole) of 2-chlorooctane (Aldrich, 99%, 16.20 mole percent, 5.83M) was substituted for 2-bromooctane. Monitoring of the reaction (Run 7, Table 8) by glc analysis (3% SE 30, 5' x 1/4", 114°C) showed a $t_{\frac{1}{2}}$ of 53 hours and a $t_{completion}$ of 768 hours. A substantial amount of tarred material remained in the distillation pot (only 58.6% isolated yield of 2-cyanooctane was obtained compared to 86.2% isolated yield of 2-cyanooctane with the bromooctane as the starting substrate). In the absence of 18-crown-6 (Run 6, Table 8), less than 5% reaction occurred under the same conditions covering

the same period of time. In Run 11, Table 8, the reaction was refluxed for 42 hours and less than 1% reaction occurred.

Displacement and Elimination Reactions Promoted by "Naked" Acetate

n-Octyl Acetate[181,182] Method I

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 10.7 g (0.0710 mole, 16.18 mole percent, 5.26M) of 1-chlorooctane (Aldrich, 99%), 1.5 g 18-crown-6 (0.0056 mole, 1.29 mole percent, 0.42M), and 2.9 ml of water (0.1671 mole, 36.71 mole percent). To this was added 19.6 g (0.2010 mole) of powdered potassium acetate (Baker) and the two-phase system was stirred vigorously at reflux temperature (pot temperature was 112-115°C). The course of the reaction (Run 1, Table 9) was monitored by glc analysis (3% SE 30, 5' x 1/4", 90°C), which showed a $t_{\frac{1}{2}}$ of 3.2 hours, a t_{end} of 10 hours, and a yield of ca. 100% of n-octylacetate. The reaction mixture was filtered (aspirator suction) and the salts remaining on the filter paper were washed with three 10 ml portions of ether. The filtrate was transferred into a 100 ml pear-shaped separatory funnel and washed twice with 10 ml portions of water. The organic phase was separated and the two aqueous phases washed twice with 10 ml portions of ether. The combined organic extracts were dried (anhydrous $MgSO_4$, 5 hours), the salt was filtered (aspirator suction), and the solvent removed by rotary evaporation (aspirator pressure). Distillation gave 11.7 g (96.4%) of n-octylacetate as a

colorless liquid: bp 98-99°C at 17 mm (lit[181] bp 210°C at 760 mm); nmr (neat, internal TMS), δ3.96 (2H triplet, J=6 cps, -CH$_2$OAc), δ1.89 (3H singlet, CH$_3$-C(=O)-O-), and δ1.7-0.5 (15H multiplet with spikes at δ1.2 and δ0.8, aliphatic -CH$_2$-); infrared (neat) 1740 cm^{-1} (ester C=O); and mass spectrum abundant fragments at m/e 112 (M^+-CH$_3$COOH) and abundant fragments at 84, 83, 70, 61, 57, 43, and 41. By glpc and nmr, no olefinic products could be detected. In the absence of 18-crown-6, utilizing approximately the same concentrations of substrates (Run 5, Table 9), less than 5% reaction occurred under the same conditions covering the same periods of time.

When the reaction was carried out with the potassium acetate completely dissolved in water (Run 3, Table 9), glc analysis (3% SE 30, 5' x 1/4", 90°C) showed a $t_{\frac{1}{2}}$ of 7.8 hours, a $t_{completion}$ of 28.2 hours, and a yield of ca. 100% of n-octylacetate. The reaction mixture was worked up exactly as reported in Run 1, Table 9. Distillation of the final product yielded 11.7 g (92.3%) of colorless n-octylacetate identified by comparison of its nmr spectra and glpc retention time with the previously identified sample of n-octylacetate.

n-Octyl Acetate, Method II

The procedure was as in Method I, except that 5.35 g (0.028 mole, 15.92 mole percent) of 1-bromooctane (Aldrich,

99%) was substituted for 1-chlorooctane. 18-Crown-6 (0.60 g, 0.0022 mole, 1.26 mole percent) and 1.1 ml water (0.060 mole, 34.64 mole percent) were added to give a final solution concentration of 4.68M in reactant and 0.36M in crown. Monitoring of the course of reaction (Run 2, Table 9) by glc analysis (3% SE 30, 5' x 1/4", 90°C) showed a $t_{\frac{1}{2}}$ of 0.67 hours, $t_{completion}$ of 1.5 hours, and a yield of ca. 100% of n-octylacetate. Distillation gave 4.5 g (94.2%) of pure n-octylacetate identified with a known sample by its glpc retention time. When the reaction was carried out in the absence of 18-crown-6 (Run 6, Table 9), less than 5% reaction occurred under the same conditions covering the same period of time.

When potassium acetate was completely dissolved in water (Run 4, Table 9), glc analysis (3% SE 30, 5' x 1/4", 90°C) showed a $t_{\frac{1}{2}}$ of 1.25 hours, a $t_{completion}$ of 3.0 hours, and a yield of ca. 100% of n-octylacetate. Distillation gave 12.7 g (96.7%) of n-octylacetate identified with a known sample by its glpc retention time.

2-Octyl Acetate,[181,182] Method I

A 100 ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser was charged with 10.7 g (0.056 mole, 16.04 mole percent, 5.60M) of 2-bromooctane (Aldrich, 99%), 1.2 g 18-crown-6 (0.0045 mole, 1.29 mole percent, 0.45M), and 2.12 ml water (0.118 mole, 35.32 mole percent). To this was added 16.35 g (0.166 mole) of powdered potassium acetate

(Baker), and the two-phase system was stirred vigorously at reflux temperature (Run 8, Table 9); pot temperature was ca. 116°C). The course of the reaction was monitored by glc analysis (3% SE 30, 5' x 1/4", 80°C) which showed a $t_{\frac{1}{2}}$ of 0.92 hour, a $t_{completion}$ of 2.67 hours, and two product peaks at $t_{retention}$ 0.8 minute (22% due to octenes) and a $t_{retention}$ of 9.5 minutes (78% due to 2-octylacetate). The $t_{retention}$ of 2-bromooctane was 6.4 minutes. Nmr analysis (CH_3CN, external TMS) showed the disappearance of the $CH_3\underline{CH}(Br)CH_2$-peak (δ 5.25), the appearance of the $CH_3\underline{CH}(OAc)CH_2$-peak (δ4.80), and the appearance of a broad multiplet for olefinic products (δ5.20). The reaction mixture was filtered (aspirator suction) and the salts remaining on the filter were washed with 10 ml portions of ether. Fifty ml of distilled water was added and the aqueous solution was extracted with three 75 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), filtered (gravity), and the bulk of the solvent removed by rotary evaporation at low heat ca. 30°C. Distillation under reduced pressure (water aspirator) gave 3.2 g (15.9%) of a fraction (olefinic products), bp 25-55°C at 24 mm and 5.7 g (72.6%) of a second fraction (2-octylacetate), bp 89-91°C at 24 mm (lit[181,182] bp 194.5 at 744 mm). Low-temperature glc analysis revealed that the low-boiling fraction was actually composed of three compounds with a distinct peak at $t_{retention}$ at 4.6 minutes (~15% of the mixture)

and a pair of overlapping peaks at $t_{retention}$ of 5.4 minutes and 5.9 minutes (~85% of the mixture). The low-temperature chromatogram overlapped in appearance and $t_{retention}$ that of an isolated and characterized mixture of 1-octene and cis-, trans-2-octene (supplied by H. P. Harris).[182] Nmr spectra (CH_3CN, external TMS) showed a broad multiplet containing five distinct peaks at δ5.20 that overlapped with the proton band of the isolated octene mixture.

The 2-octylacetate product exhibited ir absorption (neat) at 1740 cm^{-1} (ester C=O); nmr peaks (neat, internal TMS) at δ4.82 (1H sextet, -CH-OAc), δ1.82 (3H singlet, CH_3CO-), and δ1.7-5.0 (16H multiplet, aliphatic CH); and mass spectrum abundant fragments at m/e 173 (M+1) and abundant fragments at 112, 97, 87, 83, 70, 69, 59, 43, and 41. In the absence of 18-crown-6 (Run 12, Table 9), less than 6% reaction occurred under the same conditions covering the same period of time. When the reaction was carried out with the potassium salt completely dissolved in water (Run 10, Table 9), glc analysis (3% SE 30, 5' x 1/4", 102°C) showed a $t_{½}$ of 2.5 hours, a $t_{completion}$ of 11.6 hours, and good isolated yields of products.

2-Octyl Acetate, Method II

The procedure was as in Method I, except that 11.0 g (0.074 mole, 16.51 mole percent) of 2-chlorooctane (Aldrich, 99%) was substituted for 2-bromooctane. 18-Crown-6 (1.4 g, 0.0052 mole, 1.26 mole percent) and 3.0 ml water (0.167 mole,

36.7 mole percent) were added to give a final solution concentration of 5.69M in reactant and 0.41M in crown. Monitoring of the course of reaction (Run 7, Table 9) by glc analysis (3% SE 30, 5' x 1/4", 102°C) showed a $t_{\frac{1}{2}}$ of 68 hours. After refluxing for 98 hours, the reaction was stopped and glc analysis of the reaction mixture exhibited three peaks in the ratio 5:4:1 corresponding to 2-octylacetate, 2-octylchloride, and octenes, respectively. Peak assignments were based on the glpc retention times of these compounds compared to previously identified samples. No further attempt was made to isolate the various products. In the absence of 18-crown-6 (Run 11, Table 9), less than 5% reaction occurred under the same conditions covering the same period of time (actually no reaction was observed even after refluxing for 100 hours).

When potassium acetate was completely dissolved in water (Run 9, Table 9), glc analysis (3% SE 30, 5' x 1/4", 102°C) showed a $t_{\frac{1}{2}}$ of 90 hours. After refluxing for 97 hours, reaction was stopped and glc analysis of the reaction mixture exhibited three peaks in the ratio 5.5:3.5:1.0 corresponding to 2-octylacetate, 2-octylchloride, and octenes, respectively. Peak assignments were based on the glpc retention times of the various compounds compared to previously identified samples.

CHAPTER III

RESULTS AND DISCUSSION

The discovery of crown ethers along with their fascinating ability to complex the metal cation of inorganic and organic salts and solubilize them in non-polar and dipolar aprotic organic solvents is considered one of the most important discoveries of the last decade.[1-19,30-37,55-61,79-85] Thus, although metal salts are virtually insoluble in most organic solvents, the presence of catalytic amounts of crown ethers functioning as solid-liquid or liquid-liquid phase-transfer catalysts greatly facilitate synthetic transformations. Crown ethers can catalyze these reactions by solubilizing the salts and by increasing the dissociation of ion pairs to provide highly reactive "naked" anions, i.e., anions that are weakly solvated. Though utilized in synthetic reactions only since 1967,[1,2] "naked" anions have proven to be potent nucleophiles and potent bases and promise to provide a foundation for the development of synthetically useful reagents in the future.[13]

Of all the crown ethers, 18-crown-6 is the simplest and most synthetically useful.[14-16] It is the crown utilized in almost all the reactions reported in this thesis. Moreover, 18-crown-6 was found to have the ideal cavity size for accommodating the potassium ion. Therefore, it was the crown

ether of choice for generating "naked" anions from the various potassium salts reported in this thesis.

Solubilities of "Naked" Anions in Solution

The major driving forces for solubilization of alkali metal salts in crown ethers in non-polar and dipolar aprotic solvents are ΔG_1, ΔG_3, and ΔG_5 (see thermodynamic cycle, Figure 6). The different solubilities of a variety of common potassium salts in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 reported in this thesis were determined by measuring the concentration of potassium ion by flame photometry (Coleman Model-21). The order of solubilities of potassium salts in 0.15M crown-acetonitrile at 25°C is: $KSCN > KI > KN_3 \simeq KBr \simeq KCN > KOAc \gg KCl \gg KF$. Solubilities of the same salts in acetonitrile in the absence of 18-crown-6 at 25°C were likewise determined (Table 3).

It is interesting to note that the solutility enhancement is quite dramatic for KCl (228), for KOAc (204), and for KCN (108). The solubility enhancement is moderate for KBr and KN_3 (factors of 64 and 57, respectively), and marginal for KF, KI, and KSCN (Table 3). It should also be noted that KI and KSCN have high inherent solutilities in pure acetonitrile.

Along the same lines, Liotta and Harris,[94] utilizing flame photometric techniques, determined the solubility of

Table 3. Solubilities[a] of Potassium Salts in Acetonitrile at 25°C in the Presence and in the Absence of 18-Crown-6.

Potassium Salt	Solubilities of 0.15M Crown in Acetonitrile	Solubilities in Acetonitrile (without Crown)	Solubility Enhancement
1) KF	4.30×10^{-1}	3.18×10^{-4}	14
2) KCl	5.55×10^{-2}	2.43×10^{-4}	228
3) KBr	1.35×10^{-1}	2.08×10^{-3}	65
4) KI	2.02×10^{-1}	1.05×10^{-1}	2
5) KCN	1.29×10^{-1}	1.19×10^{-3}	108
6) KOAc	1.02×10^{-1}	5.00×10^{-5}	204
7) KN_3	1.38×10^{-1}	2.41×10^{-3}	57
8) KSCN	8.50×10^{-1}	7.55×10^{-1}	1.3

[a]Solubilities were measured using a Coleman Model-21 Flame Photometer.

potassium fluoride at 25°C in the dipolar and non-polar aprotic solvents, acetonitrile and benzene in the presence and in the absence of 18-crown-6 (Table 4).

It is interesting to note that the reported[94] solubility at 25°C of potassium fluoride in acetonitrile in the absence of 18-crown-6 is 3×10^{-4}; the solubility reported in our study is 3.18×10^{-4}, which compares very well with that reported earlier by Liotta and Harris.[94]

Table 4. Solubility of Potassium Fluoride in Acetonitrile and in Benzene in the Presence and in the Absence of 18-Crown-6.[94]

Solvent	(18-Crown-6), M	(KF), M
Acetonitrile	0.00	3.0×10^{-4}
	0.16	3.5×10^{-3}
Benzene	1.01	5.2×10^{-2}
	0.34	1.4×10^{-2}

Liotta and Harris,[95] utilizing nmr techniques, have also reported the solubility of potassium acetate in solutions of 18-crown-6. Solutions of the crown ether in benzene and acetonitrile-d_3 were prepared and stirred at room temperature over excess anhydrous potassium acetate for 1.5 hours. The nmr of the supernatant liquid was then taken and the concentration of acetate determined from the integration of the crown and acetate singlets. In the absence of 18-crown-6, no acetate ion could be found in the supernatant liquid. The results are shown in Table 5.

Thus, from the data reported by Liotta and Harris,[94,95] (Tables 4 and 5) it is clear that although flame photometric studies showed that the crown ether enhanced the solubility of potassium fluoride in acetonitrile by only a factor of about 10, the solubility of potassium acetate found by nmr increased by a factor of 200 in the presence of 0.14M crown.

Table 5. Solubility of Potassium Acetate in Acetonitrile and in Benzene Solutions of 18-Crown-6.[95]

Solvent	18-Crown-6(M)	Potassium Acetate(M)
Benzene	0.55	0.4
Benzene	1.00	0.8
Acetonitrile-$\underline{d}_3$	0.14	0.1

These results compare favorably with the results reported in this work.

Reactions Utilizing 18-Crown-6

All the reactions reported in this work involved a variety of common potassium salts and catalytic amounts of 18-crown-6 except for the hydrocyanation reactions of cholestenone which were carried out in a 1:1 molar ratio of cholestenone to 18-crown-6. In all cases, 18-crown-6 was utilized as a phase-transfer catalyst in solid-liquid or in liquid-liquid phase-transfer catalytic (heterogeneous) conditions. The solvents of choice were the dipolar and non-polar aprotic solvents: acetonitrile and benzene. These solvents were used since they are low boiling and inert to the "naked" anions.

Elimination Reactions Promoted by "Naked" Halides

The use of crown ethers as addends in elimination reactions as a means to determine the effect of base association has contributed tremendously to our understanding of the

course of stereospecific and regiospecific 1,2-elimination reactions. The course of these reactions with organic substrates has been the concern of a large number of workers for several decades.[92,133,135,136,155,159,183-188]

In a continuation of earlier studies by Liotta and Harris,[94,95] we have further investigated the use of "naked" halides in promoting dehydrohalogenation of 2-chloro-2-methylcyclohexanone 34, a substrate subject to "Favorskii" rearrangements, in the non-polar and dipolar aprotic organic solvents: benzene and acetonitrile. As shown in Figure 13, less than 5% reaction occurred in each of the reactions of 34 with anhydrous KF, KBr, and KI in o.15M 18-crown-6-acetonitrile solution or with anhydrous KCl in 0.15M 18-crown-6-benzene solution at room temperature. After refluxing for 6 hours, less than 5% reaction was observed with "naked" iodide or with "naked" chloride as shown by the presence of greater than 95% of the starting material as shown by glc analysis of the reaction mixture. The reactions with "naked" bromide and "naked" fluoride were complete after refluxing for 6 hours. However, "naked" fluoride gave the elimination product 2-methylcyclohexenone, in ca. 45% glpc yield (1-bromohexane, internal standard), and ca. 36% isolated yield. The substitution product 2-fluoro-2-methylcyclohexanone, was also given in ca. 32% glpc yield (1-bromohexane, internal standard), and ca. 26% isolated yield. This proved the

"naked" fluoride to be a potent base and a potent nucleophile. With the "naked" bromide however, only the elimination product 2-methylcyclohexenone, in ca. 78% glpc yield (1-bromohexane, internal standard), and in ca. 66% isolated yield, was observed with no substitution products being formed compared to the reaction with "naked" fluoride reagent. This proved the "naked" bromide reagent to be a more effective base than the other "naked" halides in promoting dehydrohalogenations on substrates subject to "Favorskii" rearrangement products. Figure 13 summarizes the results of displacement and elimination reactions of "naked" halides on 2-chloro-2-methylcyclohexanone 34.

That the reactions are faster in acetonitrile than in benzene is partly shown in the dehydrohalogenation reactions on 2-chloro-2-methylcyclohexanone with "naked" chloride in acetonitrile and in benzene solvents. In acetonitrile solvent the reaction was complete after refluxing for 21 hours, whereas in the benzene solvent less than 5% reaction was observed after refluxing for the same amount of time. The reactions are faster in acetonitrile (D=37) than in benzene (D=2) because in the former solvent the halide ion is essentially free, whereas in benzene the halide ion exists as a tight ion pair with the K^+-crown complex.[112]

In each case a fresh "naked" halide reagent was prepared by dissolving 18-crown-6 in dry acetonitrile or dry

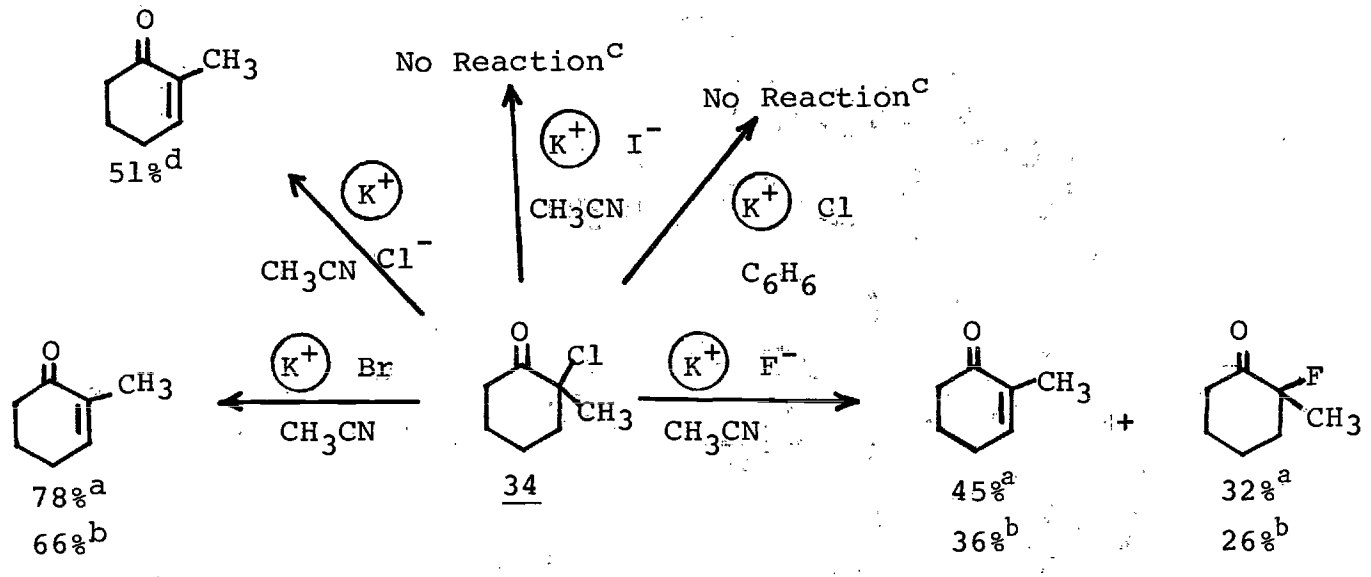


Figure 13. Displacement and Elimination Reactions of "Naked" Halides on 2-Chloro-2-methylcyclohexanone 37.

[a]Refers to percent glpc yield (1-bromohexane, internal standard).
[b]Refers to percent isolated yield.
[c]After refluxing for 21 hours, less than 5% reaction was observed with each of "naked" chloride and "naked" iodide as shown by the presence of 95% of unreacted starting material in the reaction mixture.
[d]Refers to percent isolated yield as reported by H. P. Harris.[182]

benzene and then adding dry potassium halide. After the heterogeneous system had been stirred for ≈10 minutes, the organic substrate was usually added. Progress of reaction was followed by glc analysis (3% SE 30, 100/120 varaport 30, 5' x 1/4", 80°C) using an internal standard. Less than 5% reaction was found to take place in the absence of crown under identical conditions covering the same periods of time. Moreover, in all cases reported, crown was present in catalytic concentrations indicating that it behaved as a phase-transfer catalyst in solid-liquid phase-transfer catalytic (heterogeneous) conditions.

Substitution, Elimination, and Addition Reactions Promoted by "Naked" Cyanide

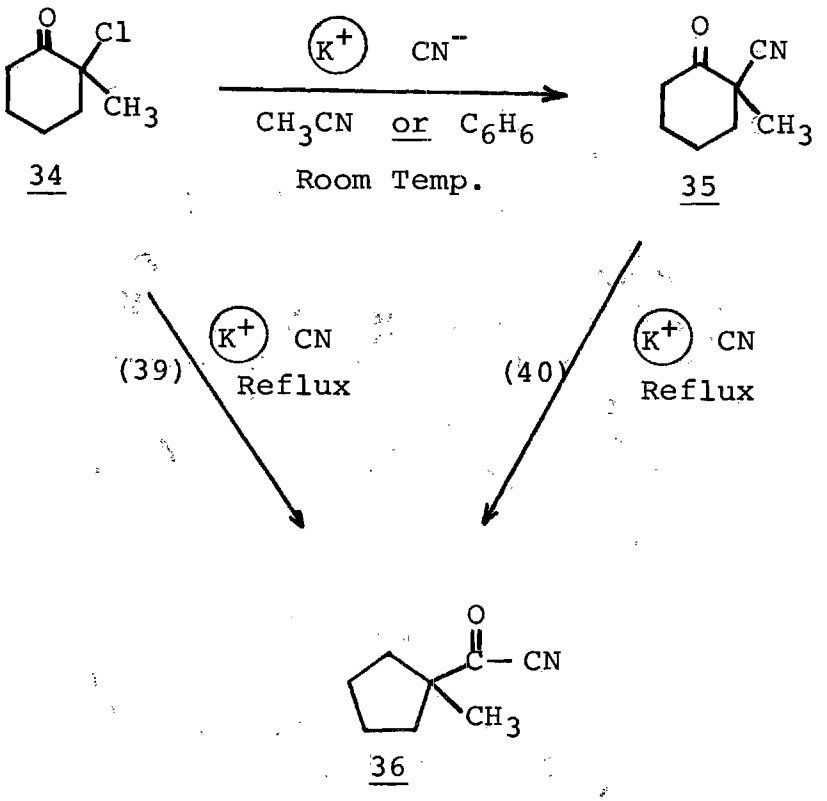
Substitutions of halides by cyanide ion have been reported to occur (i) in ethanol-water mixtures under strenuous conditions, (ii) in dipolar aprotic solvents such as DMSO,[191,192] and (iii) by use of tetraalkylammonium or -phosphonium salts to transfer the cyanide ion across a water-organic interface (phase-transfer catalysis).[89-91] Comparatively, the "naked" cyanide system[96] appears to be superior to the ethanol-water method in reaction time, temperature, simplicity of work up and yields. It also compares favorably to the dipolar, aprotic solvents and phase-transfer catalyst systems in both reaction time and yield for conversion of primary halides to nitriles.[89a-b,191-193] Advantages of the "naked" cyanide procedure over these latter methods are lower reaction

temperature and simplicity of work up. For secondary substrates, comparable yields to those presented in Appendix 12 were obtained in much shorter times in the dipolar, aprotic solvent, while the phase-transfer catalyst system gave a higher yield of substitution product (no reaction time was reported). The reaction temperatures, however, were higher in both the DMSO and the phase-transfer catalyst systems.

Reactions of "Naked" Cyanide with 2-Chloro-2-methylcyclohexanone and with 2-Cyano-2-methylcyclohexanone under Solid-Liquid Phase-Transfer Catalysis

Cyanide ion, solubilized in polar and non-polar aprotic organic solvents containing 18-crown-6 ether ("naked" cyanide) was reacted with 2-chloro-2-methylcyclohexanone 34, a substrate subject to "Favorskii rearrangement products". In thirty-five minutes at ambient temperature, the reaction proceeded to give the displacement product, 2-cyano-2-methylcyclohexanone 35, in quantitative yield (Run 1, Table 6) (Reaction 39) thus providing a potentially useful procedure for introducing a carbon functionality in a rather sterically hindered position. The effect of temperature on the course of reaction was dramatically illustrated in reactions (38 to 40). At reflux temperature, the "Favorskii rearrangement product" 36, was obtained in high yield (Run 4, Table 6) (Reaction 40). This latter product was also obtained by heating 2-cyano-2-methylcyclohexanone 35, with the inaked" cyanide reagent (Run 5, Table 6) (Reaction 39). A mechanism

which may be used to rationalize the formation of 36 is illustrated in Figure 14.



The 18-crown-6 ether was prepared by the method of Gokel and Cram in crude form and purified by the method of Harris, Cook, and Liotta.[14,15] The substrate solutions were prepared by weighing out the appropriate amount of reagent into a 25 ml volumetric flask and diluting to the mark

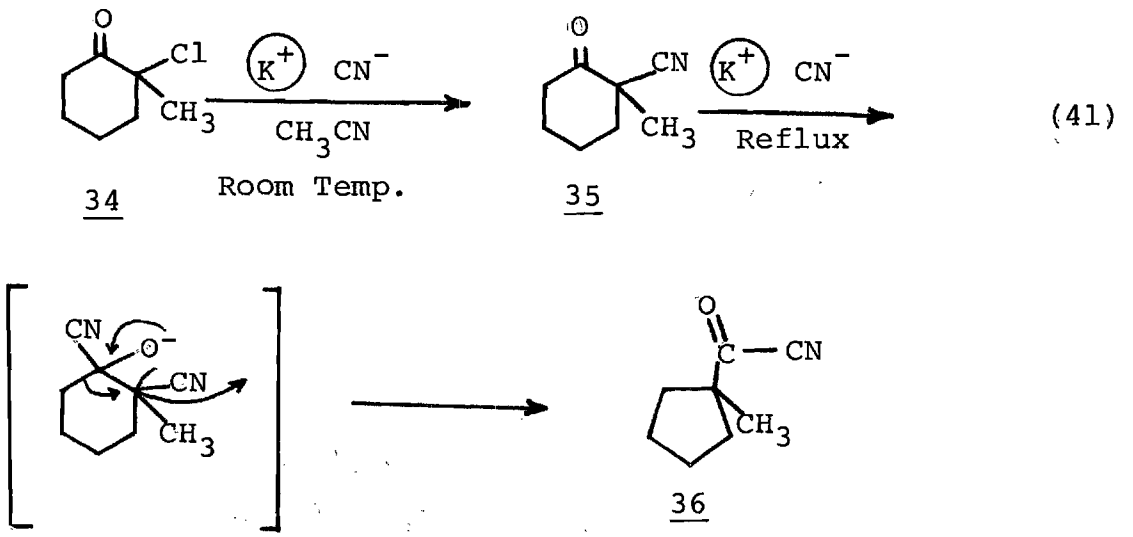


Figure 14. Mechanistic Pathway for the "Favorskii Rearrangement Product" of 2-Chloro-2-methylcyclohexanone Promoted by "Naked" Cyanide.

with a stock solution (known concentration) of 18-crown-6 in CH_3CN or C_6H_6. The prepared solutions were then placed directly over solid dry KCN (2-3 fold excess) and the heterogeneous system was stirred vigorously at ambient or reflux temperatures. Progress of reaction was followed by glc analysis. The results are shown in Table 6. In the absence of crown ether in acetonitrile solvent, the reaction proceeded slowly (Runs 1 and 3, Table 6). It is interesting to note that the reaction in the presence of crown in benzene solvent (Runs 2 and 3, Table 6) proceeded at a rate slower than the reaction of acetonitrile in the absence of crown.

Table 6. Reactions of Potassium Cyanide with 2-Chloro-2-methylcyclohexanone 34 and with 2-Cyano-2-methylcyclohexanone 35 respectively with and without 18-Crown-6 under Solid-Liquid Phase-Transfer Catalysis.

Substrate	Run	Solvent	Salt	Products	Yield[a]	Concentration (M)[b] Crown	Substrate	Temp. °C	$t_{\frac{1}{2}}$[c]	tend[d]
34	1	CH_3CN	KCN[e]	35[f]	92.1	0.18	2.60	Ambient	17 min	35 min
34	2	C_6H_6	KCN	35	90.6	0.18	2.73	Ambient	25 min	153 min
34	3	CH_3CN	KCN	35	91.2	0.00	2.32	Ambient	30 min	135 min
34	4	CH_3CN	KCN	36	60.2	0.18	2.33	Reflux	16 hrs	80 hrs[h]
35	5	CH_3CN	KCN	36	66.0	0.16	2.20	Reflux	1.0 hr	10 hrs[i]
35	6	CH_3CN	KCN	35	—	0.00	2.30	Reflux	—	—
34	7	CH_3CN	KCN	35 & 36	84.6	0.18	2.60	Ambient	17 min	35 min
35	8	C_6H_6	KCN	36	47.3	0.17	2.70	Reflux	3 hrs	31 hrs
*34	9	CH_3CN	KCN	35	—[e]	0.21	2.65	Reflux[m]	5 hrs[n]	40 hrs[n]
*35	10	CH_3CN	KCN	36	46.4	0.21	2.65	Reflux	90 hrs	—[p]
*35	11	CH_3CN	KCN	36	62.3	0.19	2.43	Reflux	7 hrs	30 hrs
35	12[g]	CH_3CN	—	35	—	0.18	2.37	Reflux	—	—

[a] Isolated yields. For all reactions with yields, glpc and nmr analysis showed a quantitative conversion to the products.

[b] The substrate solutions were prepared by weighing out the appropriate amount of reagent into a 25ml volumetric flask and diluting to the mark with a stock solution (known concentration) of 18-crown-6 in CH_3CN or C_6H_6. The prepared solutions were then placed directly over solid, dry KCN (2-3 fold excess) and the system was stirred vigorously at ambient or reflux temperature.

[c] $t_{1/2}$ is defined as the time required for 50% of the starting material to react.

[d] Estimated as closely as possible.

[e] KCN was dried in a vacuum dessicator at 105°C.

[f] Physical properties of compound 35 were as follows: B.P. 102-103°C at 23 mm. IR (neat NaCl plates) 1725cm^{-1} (C=O) and 2240cm^{-1} (C≡N). Mass spectral peaks of 137(M^+) and abundant fragments at m/e 122, 109, 97, 94, 84, 78, 69, 68, 67, 55, 54, 43, 41 and 39. H-nmr (neat, internal TMS) at δ1.55 (sharp singlet, aliphatic CH, 3H's), also at δ2.0 to 0.8 (8H multiplet, ring protons). Elemental analysis: Calculated for $C_8H_{11}NO$ (35) - C 70.04; H 8.08; N 10.21; O 11.66. Found: C 69.79; H 8.13; N 10.19; O 11.61.

[g] Physical properties of compound 36 were as follows: B.P. 108-110° at 26 mm. IR (neat NaCl plates) 1720cm^{-1} (C=O) and 2220cm^{-1} (conjugated C≡N). Mass spec. m/e 137 and abundant fragments at 122, 94, 82, 68, 67, 55, 43 and 42. Nmr peaks ($CDCl_3$, external TMS) at δ1.52 (3H singlet, $-CH_3$), at δ3.1- 1.75 (8H multiplet, ring protons). Elemental analysis: Calculated for $C_8H_{11}NO$(36) - C 70.04; H 8.08; N 10.21; O 11.66. Found: - C 70.02; H 8.15; N 10.22; O 11.61.

[h] Reaction was about 80% (glpc) complete after 40 hrs reflux.

[i] Reaction was about 95% (glpc) complete after 5 hrs reflux.

[j] Reaction was refluxed for 55 hours. No reaction was observed at all, just recovery of the starting material.

[k] When the reactions (Table 6 runs 1-3) were carried out at ambient temperature, they had to be worked out all the way at R.T. especially when evaporating the bulk of the solvent on the rotavap. When tried evaporation of the bulk of the solvent on the rotavap with the application of little heat products 35 and 36 were formed with 36 predominating presumably in the presence of traces of "naked" cyanide in the flask, compound 35 would rearrange depending on the conc. of crown, "naked" cyanide and the time of heating applied.

[l] Compound 36 once formed in reaction flask was not worked out or isolated but was left to reflux under the same conditions in the same reaction mixture in order to effect isomerization.

[m] This reaction in the presence of acetone cyanohydrin did not go at all at R.T. That is why refluxing was necessary.

[n] The reaction rate slowed down greatly after $t_{1/2}$ was reached.

[o] $t_{1/2}$ was found to be 90 hrs and after 200 hrs the reaction was only about 60% complete by analysis.

[p] The reaction was refluxed in the absence of KCN for 50 hrs and no product was shown.

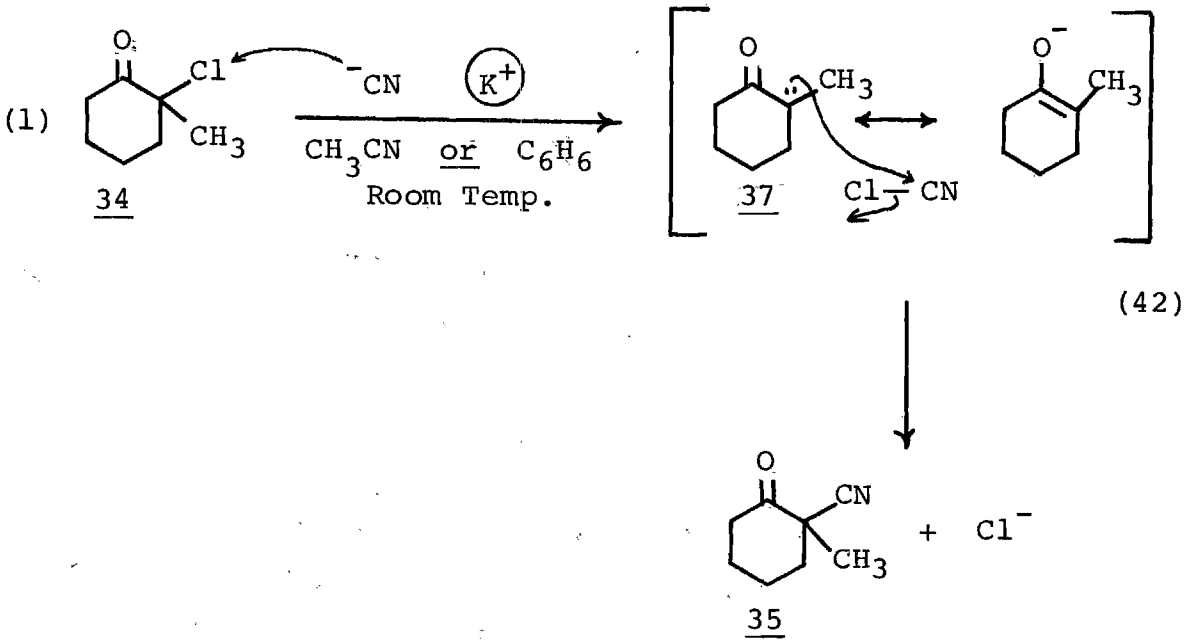
[*] Runs 1-8 were carried out in the absence of acetone cyanohydrin while runs 9-11 were carried out in the presence of 0.15M, 0.15M, 0.13M acetone cyanohydrin, respectively.

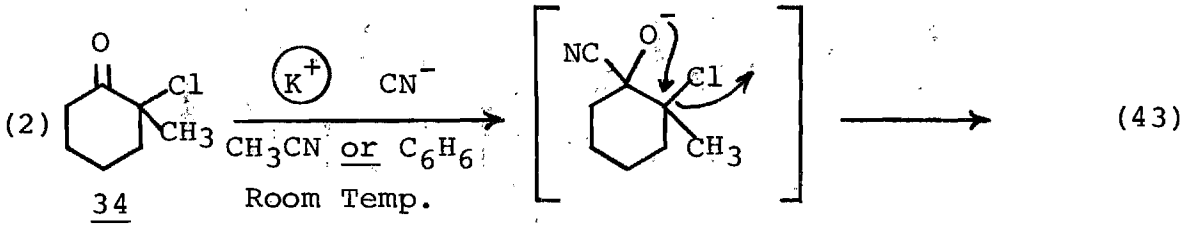
Thus, it is clear that the reaction is much faster in acetonitrile than in benzene (compare also Runs 5 and 8, Table 6). In all cases, crown was present in catalytic quantities indicating that it behaved as a phase-transfer catalyst in solid-liquid catalytic (heterogeneous) conditions. Another interesting point is that once the displacement reaction is complete (35 minutes at ambient temperature, Run 1, Table 6), the entire work up should be conducted at ambient temperature, especially when evaporating the bulk of the solvent on the roto evaporator since the displacement product has a great tendency to undergo partial isomerization to the "Favorskii rearrangement product" 36. Eventually, the presence of "naked" cyanide and the applied heat would cause the rearrangement to proceed to completion (compare Runs 1 and 7, Table 6).

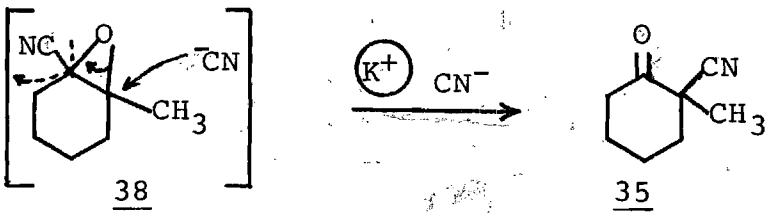
Discussion of Mechanism of the Displacement Reaction of "Naked" Cyanide on 2-Chloro-2-methylcyclohexanone

Only a few reports concerning nucleophilic substitution reactions at 3° carbon centers have appeared.[194] We have reported the reaction of "naked" cyanide with 2-chloro-2-methylcyclohexanone at room temperature in acetonitrile with the formation of the simple cyano displacement product.

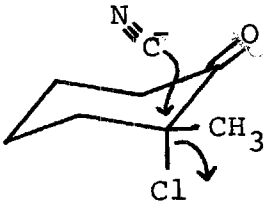
For the displacement reaction (39), the following mechanisms are proposed:







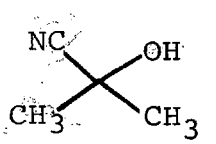
(3) Via simple S_N2 displacement mechanism (shown below). For the transformation 34 → 36, the mechanistic pathway shown in Figure (14) was proposed, however. This mechanism is discussed in detail elsewhere in this thesis.



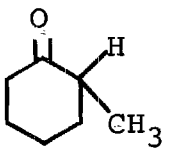
Evidences Against Mechanism (1)

(i) At ambient temperatures, 2-chloro-2-methylcyclohexanone in the presence of catalytic amounts (15%) of the proton source acetone cyanohydrin 39 gave the displacement product 35 as the only product (100% by gas chromatographic analysis of the reaction mixture). No peak due to 2-methylcyclohexanone 40 was observed. If 37 was an intermediate in the reaction (38), as proposed in mechanism (1), then it should have abstracted a proton from the acetone cyanohydrin and formed 40. This latter compound was not found under the conditions of the reaction, and, therefore, mechanism (1) was unlikely.

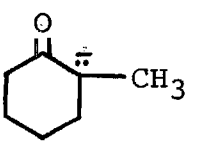
(ii) In the presence of 0.5 equivalents of acetone cyanohydrin, less than 5% reaction was affected at room temperature after stirring for 60 hours. Thus, acetone cyanohydrin seems to prevent the reaction from occurring (the reaction is otherwise complete in 35 minutes under the same conditions). Thus, mechanism (1) again failed to explain the pathway from 34 to 35 (Reaction 38). It is suggested that the acetone cyanohydrin in the presence of cyanide ion (Reaction 44) is providing the cyanohydrin intermediate 41.



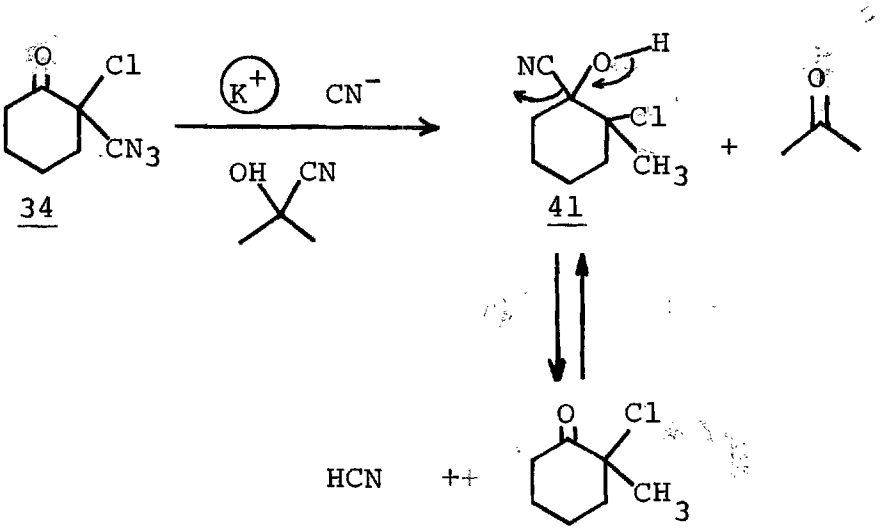
39



40



37



(44)

Thus, in the presence of acetone cyanohydrin and "naked" cyanide we are probably not dealing with an α-chloroketone which is relatively easy to displace, but actually we are dealing with a cyanohydrin which decreases the rate of displacement reaction greatly.

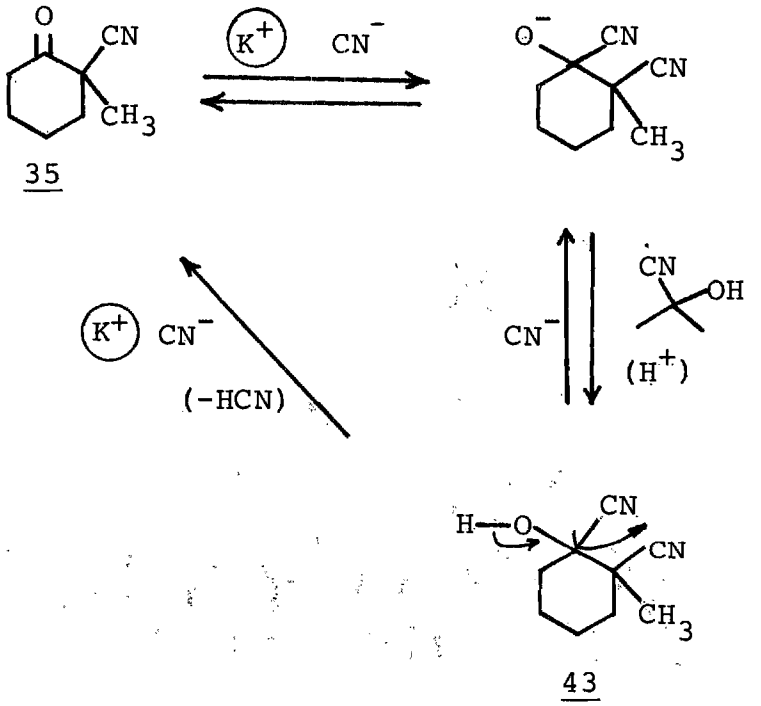
(iii) When 40 was added to the reaction mixture toward $t_{\frac{1}{2}}$ of the reaction (ca. when about 50% of the starting material had been converted to product), it did not undergo any change whatsoever but stayed exactly with the same starting concentration in solution. Thus, if any of compound 40, in the presence of acetone cyanohydrin, was formed in any stage of the reaction proposed in mechanism (1), then it would have stayed in solution without undergoing any change whatsoever. That did not seem to be the case, however. Therefore, mechanism (1) was discarded.

Evidences for the "Favorskii Rearrangement" Mechanism, the Transformation 34 to 36 (Figure 14)

(i) In the absence of KCN, refluxing of compound 35 for 50 hours in the presence of crown ether and acetonitrile solvent did not affect isomerization. The cyanide ion, therefore, is essential for the isomerization step to occur (Run 12, Table 6).

(ii) In the absence of crown ether, refluxing of compound 35 for 55 hours in the presence of KCN and acetonitrile solvent did not effect isomerization. All of the starting material remained unaltered. This suggests the important catalytic effect of 18-crown-6 in solubilizing the KCN salt and thus generating enough of the "naked" cyanide reagent which attacks the substrate 35 and leads to the isomerization product 36 (Run 6, Table 6).

(iii) In the presence of acetone cyanohydrin, the rearrangement reaction 35 to 36 was found to slow down greatly. Thus, after refluxing for 90 hours only 50% of 35 had isomerized. The same reaction, however, when carried out in the absence of acetone cyanohydrin was found to reach $t_{\frac{1}{2}}$ after refluxing for 1.0 hour only (compare Runs 5 and 10, Table 6). The effect of acetone cyanohydrin on the rate of the reaction is, therefore, dramatic. This effect may be due to the protonation of the intermediate involved in this mechanism and leading to 43. Thus, in the presence of the proton source (acetone cyanohydrin) the following equilibrium may be present (Reaction 45).



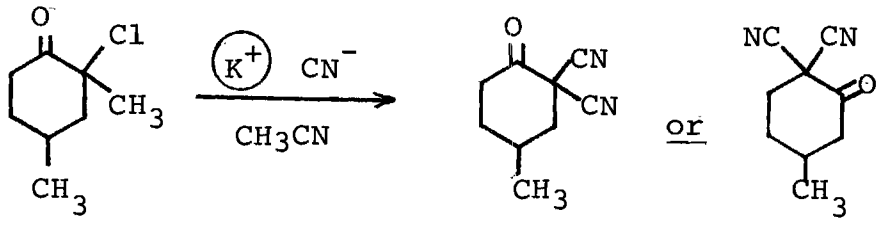
(45)

35

43

Studies on Mechanism (2)

In order to study the pathway involved in the transformation of 34 to 36 (reaction 39), the following reaction was suggested (Reaction 46).



(46)

44

45[164]

or

46[164]

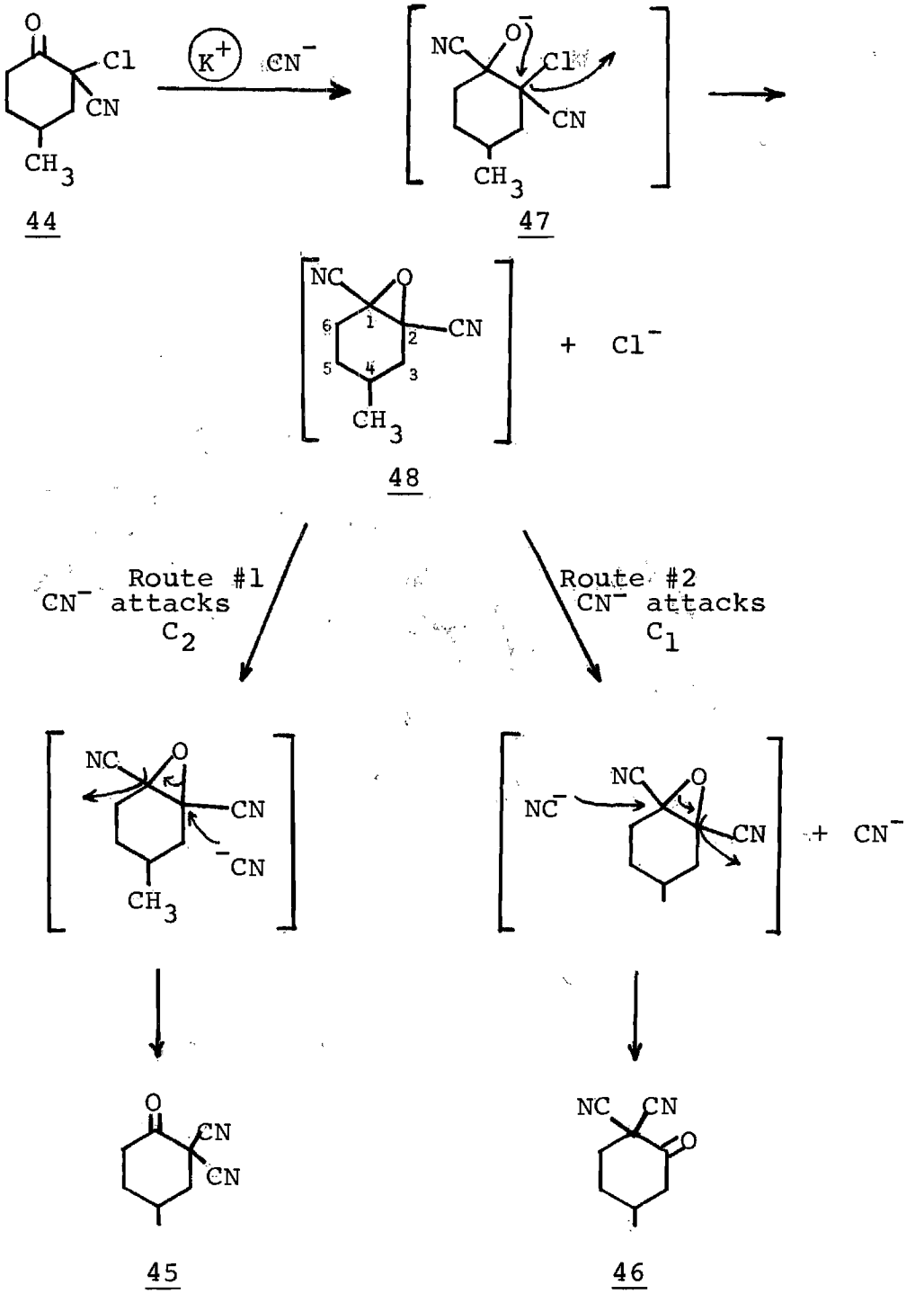
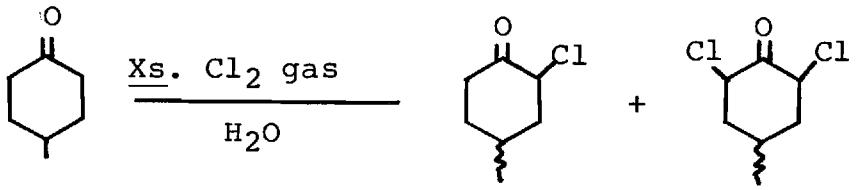


Figure 15. Proposed Mechanism for the Reaction of "Naked" Cyanide with 2-Chloro-2-cyano-4-methylcyclohexanone.

Some difficulties were encountered in the preparation of the monochloro compound. When using a stoichiometric amount of sulfuryl chloride about 45% of the starting material remained unreacted. Upon addition of more sulfuryl chloride in carbon tetrachloride (ca. 1.2 moles), all the starting material was converted to the products with the ratios indicated above (Reaction 47). Attempted separation, under vacuum distillation, of the monochloro compound from the dichloro compounds failed due to their close boiling points. Distillation of the mixture under atmospheric pressure, however, left a brown, viscous, polymeric material. Separation of another fraction from a different run using the spinning band gave the pure monochloro compound in poor yield with the major fraction of the monochloro compound contaminated by the dichloro compound in varying ratios. Nonetheless, enough pure sample of the monochloro compound was obtained to carry out a few reactions, which will be discussed subsequently.

Another procedure was utilized for the preparation of the monochloro compound. In this procedure, excess chlorine gas was bubbled into aqueous 4-methylcyclohexanone (Reaction 48).

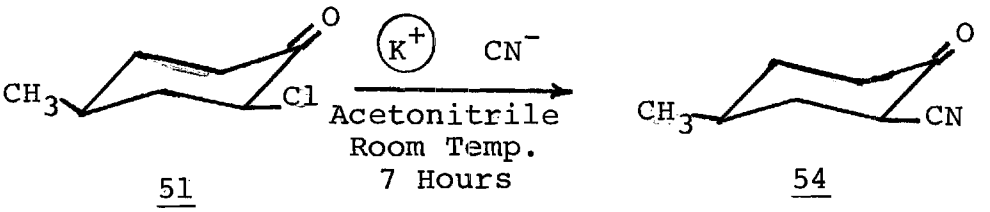
Following the procedure reported in Organic Synthesis,[167-169] less than 30% of the mixture of chlorination products was obtained with the dichloro compound 53



50 51 (70%) 53 (30% by glc)

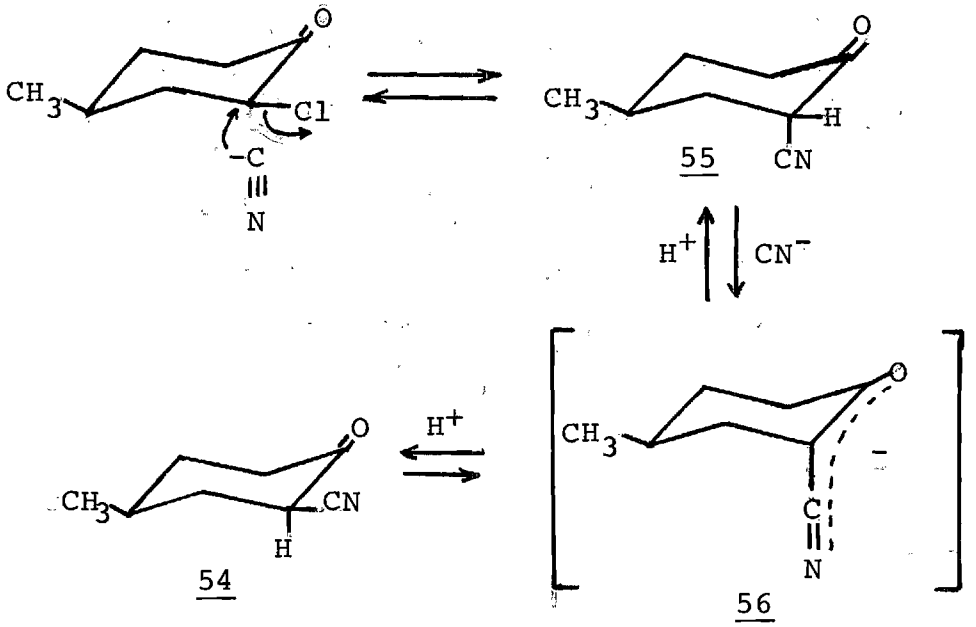
predominating. The procedure suffered from back suction of water from the trap. A modified synthesis of the monochloro compound (see experimental) was utilized and was found to give ca. 70% of the desired monochlorination products in a stereoselective manner (i.e., the cis-isomer, cis-2-chloro-4-methylcyclohexanone comprised > 95% of the mixture of cis- and trans-2-chloro-4-methylcyclohexanones).

The reaction of cis-2-chloro-4-methylcyclohexanone with the "naked" cyanide reagent in acetonitrile at room temperature for seven hours resulted in a quantitative conversion to the displacement product, cis-2-cyano-4-methylcyclohexanone. The final product gave only one peak, 100% by glc analysis (3% SE 30, 5' x 1/4", 103°). Nmr spectra confirmed the product to be the cis-cyano compound. The identity of the compound was further furnished from ir spectra, mass spectral analysis, and elemental analysis (Reaction 49).



51 (>95% cis-isomer) 54 (100% cis-isomer) (49)

Several mechanisms may be written for reaction (49). A possible mechanism could be S_N2 followed by equilibration (Reaction 50).

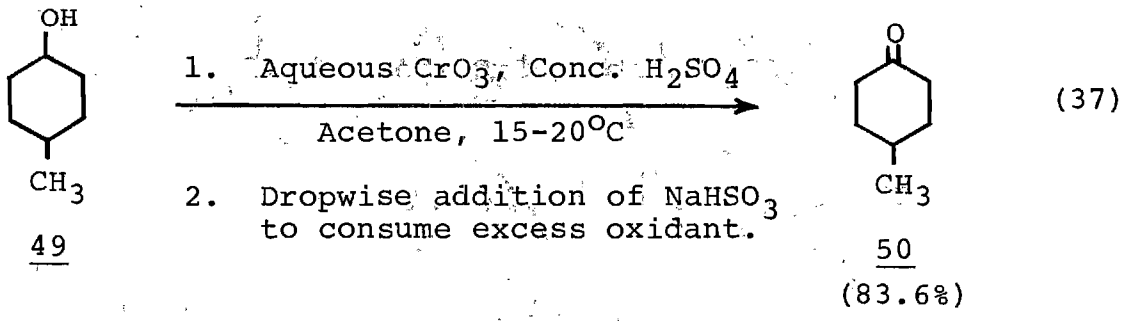


(50)

Along the same lines, Kohli[195] had shown that optically active 1-chloro-1-phenyl ethane reacted with "naked" cyanide reagent to give a racemic mixture of 1-cyano-1-phenyl ethane (Figure 16).

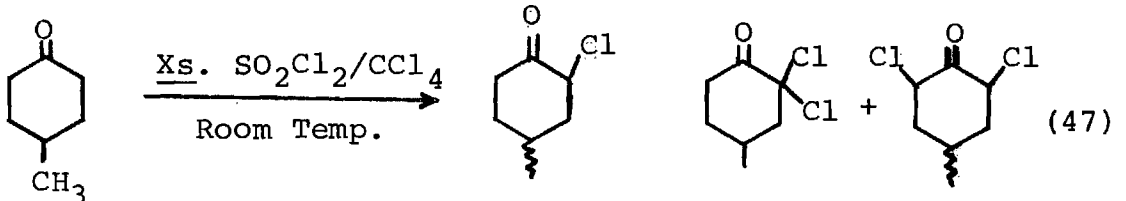
The formation of either 45 or 46 from 44 will give a clue regarding the validity of the "epoxide mechanism" [mechanism (2), Reaction 43] proposed for the transformation of 34 to 35 (Reaction 39).

In order to study the mechanism proposed in Figure 13, 4-methylcyclohexanone 50 was prepared from 4-methylcyclohexanol 49 by a previously reported procedure[165] (Reaction 37).

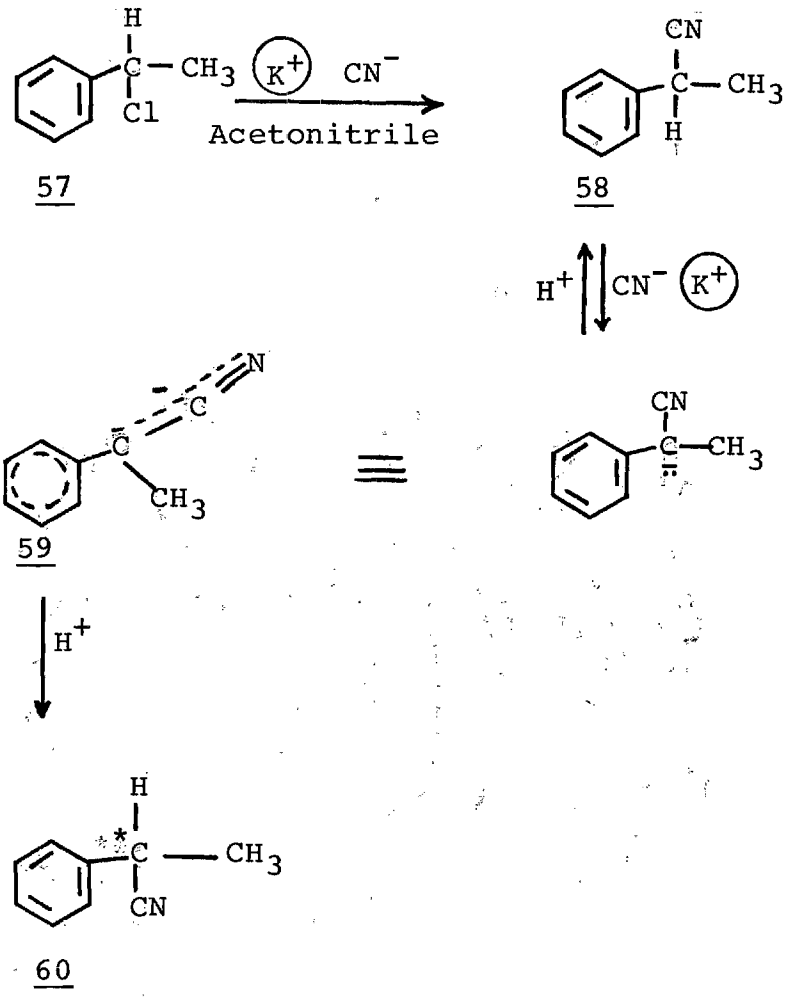


49 50 (83.6%) (37)

From 50 we set out to prepare 2-chloro-4-methylcyclohexanone 51 (Reaction 47).



50 51 (43%) 52 (10%) 53 (47% by glc) (47)



(51)

(Racemic Mixture)

Figure 16. Racemization of Optically Active 1-Chloro-1-phenyl ethane 57 with "Naked" Cyanide-Acetonitrile Solution.

In both cases, the initial step involves S_N2 displacement of chloride ion by "naked" cyanide to give the cyanide displacement product. This product, which has a highly acidic proton, undergoes racemization via abstraction

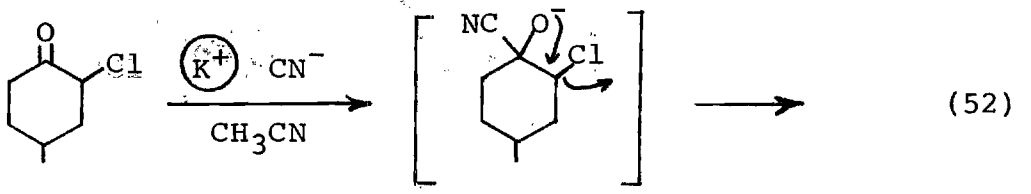
of the acidic proton by the cyanide ion to form the intermediate 59 followed by equilibration to 60.

The S_N1 mechanism, on the other hand, is questionable and compared to the reaction of "naked" cyanide with 2-chloro-2-methylcyclohexanone, "naked" cyanide displaced tertiary R-Cl much faster than secondary R-Cl (35 minutes versus 7.0 hours for complete reactions). This observation is contrary to normal expectations.

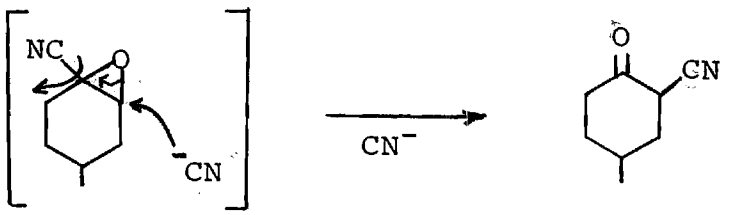
In S_N2 mechanistic reactions the following order of displacement of alkyl halides is usually observed: 1^{o} R-Cl$\gg$ 2^{o} R-Cl $\geq$ 3^{o}R-Cl; where the primary alkyl halides are the most easily displaced by nucleophiles, whereas the tertiary alkyl halides are the least easily displaced (in fact the tertiary alkyl halides are expected to be displaced by the S_N1 and not by the S_N2 mechanism). Since both substrates, 2-chloro-2-methylcyclohexanone and 2-chloro-4-methylcyclohexanone underwent displacement reactions with the latter reaction proceeding to product with complete retention of configuration, it is thought that the same mechanism should be operating in both reactions. Thus, a possible mechanism that could explain both displacements by "naked" cyanide on 2-chloro-2-methylcyclohexanone 34 (Reaction 39) and on cis-2-cholro-4-methylcyclohexanone 51 (Reaction 49) could be S_N2 followed by equilibration. Thus, the pathway for reaction (49) could be explained by the scheme in reaction

(50). The pathway for reaction (39) could also be explained similarly.

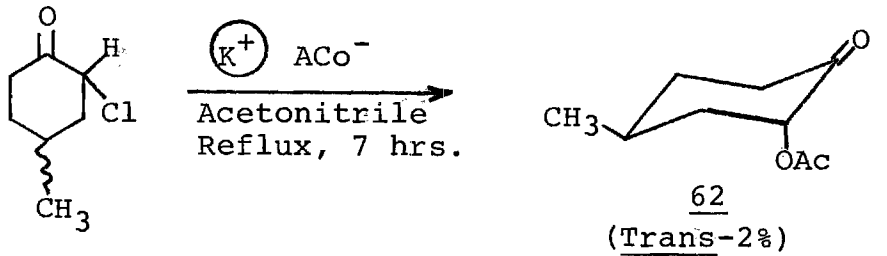
Another possible mechanism that could explain the above displacement reactions (39 and 40) would involve an epoxide intermediate depicted in reactions (43 and 52) for reactions (39 and 49), respectively. Thus, these two possible mechanisms, the S_N2 followed by equilibration mechanism and the "epoxide" mechanism would explain the retention of configuration in the reaction of "naked" cyanide with 2-chloro-4-methylcyclohexanone. They would also explain the facile nucleophilic substitution on 2-chloro-2-methylcyclohexanone. Further, the two possible mechanisms would also explain the complete retention of configuration (ca. 96%) obtained in the displacement reaction of "naked" acetate on 51 (Reaction 53).



(52)



61 54

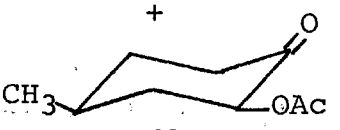


(53)

62
(Trans-2%)

Cis/Trans = 1.4

+



63
(Cis-96%)

+ 2% Alkenes

Addition Reactions Performed with "Naked" Cyanide and Acetone Cyanohydrin

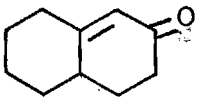
The versatility of the "naked" cyanide reagent in addition reactions to α,β-unsaturated ketones is demonstrated in the smooth and stereospecific hydrocyanation of Δ^4-cholesten-3-one in the presence of acetone cyanohydrin.

Conjugate Hydrocyanation of α,β-Unsaturated Ketones

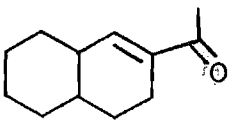
Historical

The conjugate hydrocyanation of α,β-unsaturated ketones having a bridgehead β-carbon atom (angular position) or a nonbridgehead β-carbon atom (nonangular position) in the octalene and hydrindene systems has been subject to intensive

investigation in the last two decates.[196,197] Of interest has been the introduction of a nitrile group at an angular position by the conjugate addition of potassium cyanide to α,β-unsaturated ketones[198] (resulting in C-5 cyano ketones) especially the steroids and terpenoids. C_5-cyano-steroids have been of particular interest to chemists mainly to study the effect of electronegative groups on the biological activity of steroid hormones.[198] The potential of conjugate addition was first realized by Robinson[199] who examined cuprous bromide-catalyzed 1,4-addition of the methyl iodide Grignard reagent to $\Delta^{1,9}$-2-octalone 64. The reaction proceeded in a highly stereoselective manner to give 60% isolated yield of cis-9-methyl-2-decalone.[200] Meyer and Wolfe[201] examined addition of hydrogen cyanide to 1-acetyl-$\Delta^{1,8}$-hydrindene 65. The latter was hydrocyanated in aqueous KCN/DMF/NH_4Cl system and produced a mixture of 4-racemates as the hydrocyanation products.



64



65

Several methods of hydrocyanating α,β-unsaturated ketones have been utilized in the last two decades. Most notably are:

(a) Excess KCN in 95% EtOH (MeOH),[173,200] reflux (≲10 hrs).

(b) Aq. KCN/NH_4Cl/DMF,[203,204] reflux (≲10 hours).

(c) $Ca(CN)_2$/N-Methyloyrrolidone,[205] room temperature (≃50 hours).

(d) AlR_3/HCN (THF),[173,203,206] room temperature (≲10 hrs).

(e) Et_2AlCN (THF, CH_2Cl_2, ether, or C_6H_6),[173,203,206] room temperature (≲10 hours).

Methods (a), (b), and (c) will be referred to as the conventional methods while methods (d) and (e) are the most recent hydrocyanation procedures developed and utilized by Nagata et al.[173,203,206] As regards the merits of each procedure mentioned above, procedure (a) has proven to be unsatisfactory because it involves undesirable side reactions such as hydrolysis, dimerization, and competitive, 1,4-addition of protic solvents. Procedure (b) allows the reaction to be maintained at minimal basicity thus preventing hydrolysis and dimerization. This procedure (b) has proven to be suitable for the introduction of a cyano group into a bridgehead β-carbon atom (angular cyanation) of various polycyclic systems and has been successfully applied to the synthesis of natural products, modified steroids, and other polycyclic carbonitriles.[173,205,207] This procedure, however, is still found unsatisfactory both in efficiency and stereoselectivity. Procedure (c) gives reasonably good yields of cyano-compounds, but has two disadvantages: (i) undesirable side products, and (ii) when using wet $Ca(CN)_2$ and/or wet

N-methylpyrrolidone a mixture of α- and β-Lactams was produced.[174-178]

Following this, Nagata et al.[202] outlined the requirements for a good hydrocyanation reagent: (i) The reagent should be soluble in aprotic solvents to avoid formation of solvolysis products; (ii) it should be only slightly basic or non-basic to prevent isomerization or dimerization of both substrates and products; (iii) it should be capable of activating the α-enone system sufficiently (a high concentration of cyanide anion or its equivalent species may be more important than strong activation of the α-enone function for effective hydrocyanation); and (iv) it should have or produce a cyanide species.[202]

With this outline in mind and the fact that alkyl groups attached to aluminum do not add to the carbonyl function readily but do effect liberation of cyanide anion, Nagata found the alkyl aluminum cyanides to be potent reagents for hydrocyanation. His two new methods of hydrocyanation (d) and (e) using alkyl aluminum compounds resulted in high efficiency, high uniformity, high selectivity, and high stereoselectivity. In other words, difficulties encountered in conventional methods on steric and electronic grounds are overcome, undesirable side reactions hardly occur, and the reaction can be carried out in the presence of other functional groups. Thus, smooth introduction of an angular cyano

group into many sterically hindered bridgehead carbons indicates that the steric requirement of the cyanating species in Nagata's methods is considerably smaller than that in the conventional methods and that of the Grignard reagent. Nevertheless, the steric effect is an important factor to effect the rate of the conjugate hydrocyanation.[196,197] Side reactions such as hydrolysis and dimerization hardly occur in the new methods (d) and (e). Moreover, compounds susceptible to acids and bases fail to be hydrocyanated by the conventional methods, but successful with the neutral reagent Et_2AlCN.[173,203,206] Also, while method (d) is irreversible, and gives kinetically controlled products, method (e) is reversible, and, if allowed for prolonged times will give thermodynamically controlled products. But because of its reversible nature, method (e), which is considered more efficient than method (d), does not go to completion in certain cases where the β-carbon of the enone system is electrically or sterically deactivated. This represents a major disadvantage to method (e). Thus, Nagata's reagents need to be modified in a way so as to give higher stereoselectivity in products especially in angular cyanation of polycyclic α,β-unsaturated ketones where the trans- to cis- product ratio is an important stereochemical requirement.

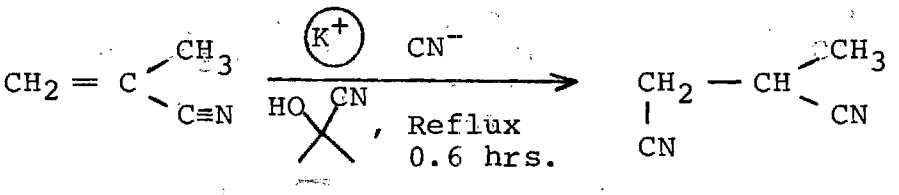
Thus, Nataga's hydrocyanation methods have been applied successfully to conjugate hydrocyanation of the following α,β-unsaturated ketones to the corresponding β-cyano ketones:

mesityl oxide, cyclohexanone, bi- and tricyclic enones, and steroidal enones.[173,196,203,206] The most useful application of these methods is conjugate hydrocyanation of α,β-unsaturated ketones. The choice of the reagent and reaction conditions depends on structures of enones and affects the stereoselectivity in angular cyanation of polycyclic enones.

Of particular interest of the α,β-unsaturated ketones among researchers has been Δ^4-cholesten-3-one[198,208] (conventional name, cholestenone) 66 and its derivatives. Conjugate addition to cholestenone was first considered by M. Musgrave[209] who examined the action of a Grignard reagent (CH_3MgI) on cholestenone. The only product was 3-methyl-cholest-4-ene-3-ol produced by 1,2-addition. When the reaction was run in the presence of cuprous chloride catalyst, however, 3-methyl-cholesta-3:5-diene formed. Thus, 1,4-addition to cholestenone was not observed in both cases. Literature reveals that the action of a Grignard reagent on cholestenone produced only 1,2-addition products and not the anticipated 1,4-addition product.[210] This clearly shows that in the case of a sterically hindered C-5 position, the introduction of a bulky substituent, such as the solvated Grignard reagent,[209] is difficult. Conjugate addition to cholestenone was reconsidered early in the last decade when Nagata et al.[211] attempted the 1,4-addition of the small, yet sufficiently nucleophilic CN^- ion on cholestenone. Since then Nagata et

al.[203,206,173] and other workers have published a considerable work on the hydrocyanation of cholestenone and various other polycyclic compounds. The various methods of hydrocyanation of cholestenone are included in Appendix 7 with the merits of each method discussed.

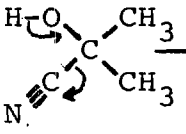
Recently, Liotta, Cook, and Bowers[96] reported the hydrocyanation of methacrylonitrile. The reaction proceeded readily in the presence of acetone cyanohydrin (used in slight excess to reagent, and utilized as a proton donor and as a cyanide ion regenerator) to give a quantitative yield of 1,2-dicyanopropane (Reaction 54).



(54)

It is interesting to note that when the above reaction was carried out in the absence of acetone cyanohydrin reagent, the "naked" cyanide ion added reversibly to the carbon-carbon double bond and no product was observed (Appendix 3, Run 12). However, in the presence of acetone cyanohydrin, the reaction proceeded smoothly and quantitatively to products. This may be visualized in the following sequence for the reactions with acrylonitrile:

(1) $CH_2 = CH-C\equiv N + :CN^- \rightleftharpoons CH_2-C\bar{H}-CN$ (CN)

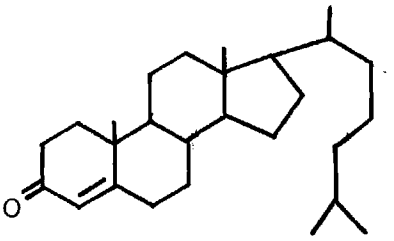
(2) $CH_2-C\bar{H}-CN$ (CN) +  $\rightarrow CH_2-CH_2-CN$ (CN) + $(CH_3)_2C=O$ + CN^-

(3) Repeat (1) and (2)

Previously, acetone cyanohydrin has been used to hydrocyanate methacrylonitrile, but the rate was much slower than in the presence of "naked" cyanide[180] (Appendix 6).

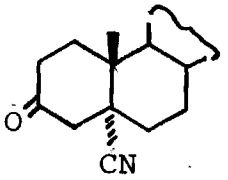
This same procedure reported earlier by Liotta, Cook, and Bowers[89] has been applied to the hydrocyanation of cholestenone (Reaction 55). The results are summarized in Table 7. Thus, in the presence of acetone cyanohydrin, "naked" cyanide undergoes stereoselective Michael addition to Δ^4-cholesten-3-one, 66, to give a mixture of α- and β-isomers, 67 and 68, respectively.

The generalized hydrocyanation procedure consists of simply pouring the substrate-crown solution directly over excess, dry KCN. Acetone cyanohydrin is then added and the two-phase system is stirred vigorously. The reaction mixture is then filtered, the solvent evaporated and the mixture of cyano products isolated. The isomeric (α- and β-) cyano products are separated from each other using standard column



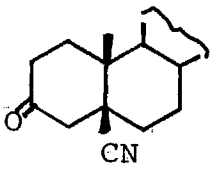
66

(55)



5α-isomer

67



5β-isomer

68

chromatography procedures. The results and the specific details of the experimental procedure are summarized in Table 7. Excellent isolated yields of hydrocyanation products are obtained in benzene and in acetonitrile (83-86%), and no cyanide hydrolysis product (amides or lactams) or dimers could be detected. The isolated yields of the individual isomers are also excellent and are indicated in Table 7. In addition, the following observations and conclusions could be drawn from the work reported in this thesis:

1) No reaction occurred in either CH_3CN or C_6H_6 in the absence of crown under the same conditions (Table 7,

Runs 1 and 6) while the reaction was complete in the presence of crown in a few hours (Table 7, Runs 2, 3, 4, 5, 7, and 8). Thus, the important effect of 18-crown-6 in solubilizing the potassium salt and facilitating Michael addition with the "naked" cyanide was demonstrated.

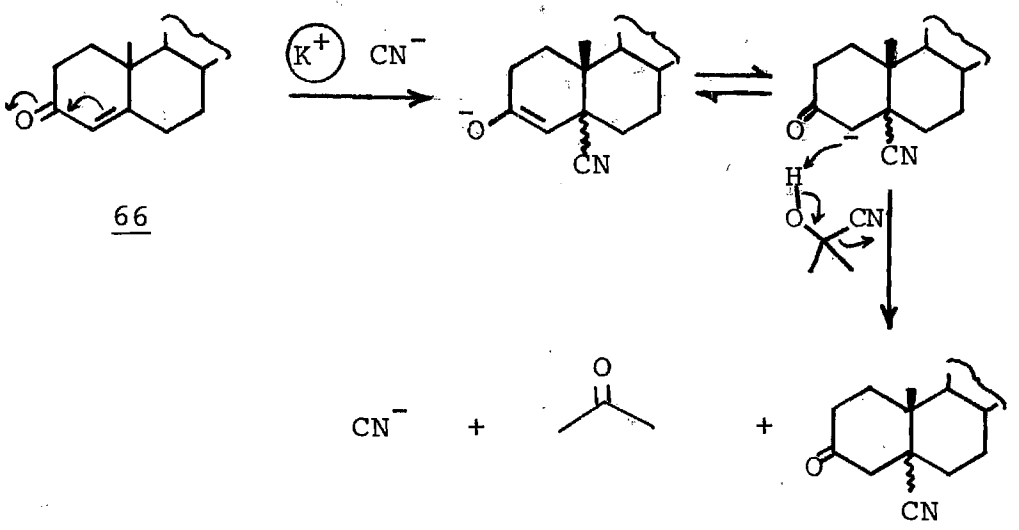
2) In Run 2, Table 7, the ratio of 5α/5β is 1/10 and the reaction is complete in 15 hours (ambient temperature). Nagata et al.[173] reported a ratio of 5α/5β of 1/9 (where the 5α-isomer is the kinetic product and the 5β-isomer is the thermodynamic product). However, the mild reaction conditions reported herein are preferable to the conditions reported by Nagata's group [hydrocyanation of 66 with Et_2AlCN and benzene, room temperature (Argon), 51 hours to equilibration].[173] In addition, undesirable side products were usually obtained in the earlier reports, and the cyano ketones were generally synthesized in a non-stereoselective manner (1:1 ratio of 5α/5β).[173,196,200,202,205,206,212,213]

3) The ratio of 5α/5β changes from 1/10 to 1/4.7 to 1/3.6 as the temperature of reaction progresses from ambient to 52° to reflux. Apparently, the more thermodynamically stable product is formed at the lower temperature. This agrees very well with Nagata's findings also.

4) The yields of isolated products (82-86%) compare favorably with those reported in the literature.[173,196,200,202,205,206,212,213]

5) The starting material, 66, is extremely soluble in C_6H_6 at room temperature, but is only slightly soluble in CH_3CN below reflux. Hence, the reaction in C_6H_6 is complete in 15 hours at ambient temperature while with CH_3CN the reaction is only 60% complete after 20 hours at 52°C (Runs 2 and 9, Table 7).

6) With catalytic amounts of KCN, the reaction is only 50% complete after 7 hours at reflux in CH_3CN while with stoichiometric KCN the reaction is complete in five hours. This is in contrast to the hydrocyanation of methacrylonitrile previously reported where catalytic KCN was enough to drive the reaction to completion.[180] The steroid compounds, however, are bulky, and a large concentration of "naked" cyanide is needed to speed up the hydrocyanation reactions. KCN presumably initiates the reaction as shown below:



66

Table 7. Hydrocyanation of Δ^4-Cholesten-3-One, 66, with "Naked" Cyanide and Acetone Cyanohydrin under Solid-Liquid Phase-Transfer Catalysis.

Run	Solvent	[Yield][a,b]	Ratio 5α/5β	KCN[c]	Concentration (M) Crown	Substr.	Reaction Temp. °C	React.[d] Time Hr	Tend[e] Hours	Results[f] [1,2]
1	C_6H_6	---	---	stoich.	0.00	0.15	Reflux	32	---	No Reaction
2	C_6H_6	[83.6] 5α-(7.0) 5β-(7.0)	1/10[h]	2xstoich[h]	0.19	0.14	Ambient	15	15	Reaction Complete
3	C_6H_6	[82.8] 5α-(13.2) 5β-(62.1)	1/4.7	2xstoich.	0.17	0.16	52°	10	10	Reaction Complete
4	C_6H_6	[84.3] 5α-(18.0) 5β-(56.8)	1/3.16	stoich.	0.19	0.16	Reflux	3	3	Reaction Complete
5	C_6H_6	[85.1][i] 5α-(15.0) 5β-(60.1)	1/4.0	catalytic	0.10	0.16	Reflux	5	5	Reaction Complete
6	CH_3CN	---	---	stoich.	0.00	0.16	Reflux	80	---	No Reaction[j]
7	CH_3CN	[84.4] 5α-(15.4) 5β-(60.6)	1/3.9	stoich.	0.19	0.14	Reflux	5	5	Reaction Complete

Table 7 (Continued)

Run	Solvent	[Yield][a,b]	Ratio 5α/5β	KCN[c]	Concentration(M) Crown	Concentration(M) Substr.	Reaction Temp °C	React.[d] Time Hr	Tend[e] Hours	Results[f] 1,2
8	CH_3CN	[86.12] 5α-(14.7) 5β-(61.4)	1/4.2	stoich.	0.21	0.15	Reflux	10	5	Reaction was complete in 5 hr; allowed to proceed further
9	CH_3CN	[48.8] 5α-(6.10) 5β-(32.1)	1/5.3	2xstoich.	0.20	0.13	52°	20	---[k]	Run allowed to proceed only to 60% completion
10	CH_3CN	[41.2] 5α-(6.90) 5β-(29.7)	1/4.3	catalytic	0.19	0.14	Reflux	7	---[l]	Run allowed to proceed only to 50% completion
11	CH_3CN	---	---	---[m]	0.20	0.15	Reflux	35	---	No Reaction
12	C_6H_6	---	---	stoich.[n]	0.19	0.16	Reflux	31	---	No Reaction

[a]Numbers in squared-brackets refer to percent isolated yield as collected from column chromatography.
[b]Numbers in parentheses refer to percent isolated yield of each isomer (separately) after recrystallization.
[c]Catalytic KCN is ≈10% KCN while stiochiometric KCN is 1.0 equivalent KCN to 1.0 equivalent of substrate to 1.2 equivalent acetone cyanohydrin except in cases when 2xstioch. KCN was used in which case 1.2 (2xstoich.) acetone cyanohydrin was used.
[d]For those runs with reaction time > 5 hrs., an aliquot sample was analyzed by nmr techniques every 2 hrs. for the first 10 hrs., and every 5-10 hrs. later on.

Table 7 (Continued)

[e]Estimated.

[f1]In all cases progress of reaction was followed by nmr techniques following the disappearance of vinyl proton band in the 4-6 ppm region.

[f2]Attempts to follow progress of reaction by glc analysis using 2% SE30 on chrom. Q, 60/80 mesh, column temp. 212°C were unsuccessful because at such high temperatures the cyano-products would lose HCN easily to produce starting material.

[g]This is the best ratio of trans/cis products ever reported.

[h]When using 1xstoichiometric KCN the reaction was ≃ 80% complete after stirring at ambient temperature for 30 hrs.

[i]IR's, nmr's, ORD's, mp's and elemental analyses for the 5-cyano ketones isolated from all runs were consistent with the reported structures.

[j]In the absence of crown ether no reaction occured even after refluxing for prolonged times (runs 1 and 6).

[k]In run 9, ≃ 35% of the starting material was recovered.

[l]In run 10, ≃ 40% of the starting material was recovered.

[m]This run was carried out in the presence of crown ether and acetone cyanohydrin but in the absence of KCN. The reaction was refluxed for 35 hrs. but no reaction occurred.

[n]This run was carried out in the presence of crown ether and KCN but in the absence of acetone cyanohydrin. The reaction was refluxed for 31 hrs. but no reaction occurred.

The Michael addition of "naked" cyanide to cholestenones is the first stereoselective application of the procedure. Particularly striking is Run 2, Table 7, which gives a ratio of 1/10 in favor of the 5β-isomer. Hence, the potential synthetic value of the mild and facile stereospecific route is apparent.

The hydrocyanation of Δ^4-cholesten-3-one was attempted using silver cyanide salt, crown ether and acetone cyanohydrin. The results of the hydrocyanation reaction utilizing this system were not promising, however. The reaction was stopped after refluxing for 20 hours and was not studied any further. It appears that AgCN is extremely insoluble even in the presence of crown.

On the other hand, hydrocyanation reactions of $\Delta^{4(10)}$-octalin-3-one 71 (see Figure 17 for preparation) and of 9-methyl-$\Delta^{4(10)}$-octaline-3-one 75 with the "naked" cyanide-acetone cyanohydrin reagent proceeded very smoothly in benzene at room temperature and, added to the initial results on the stereoselectivity of the addition reaction using the above reagent, gives a powerful evidence to the versatility of "naked" cyanide-acetone cyanohydrin as a simple, efficient, and new hydrocyanating reagent.

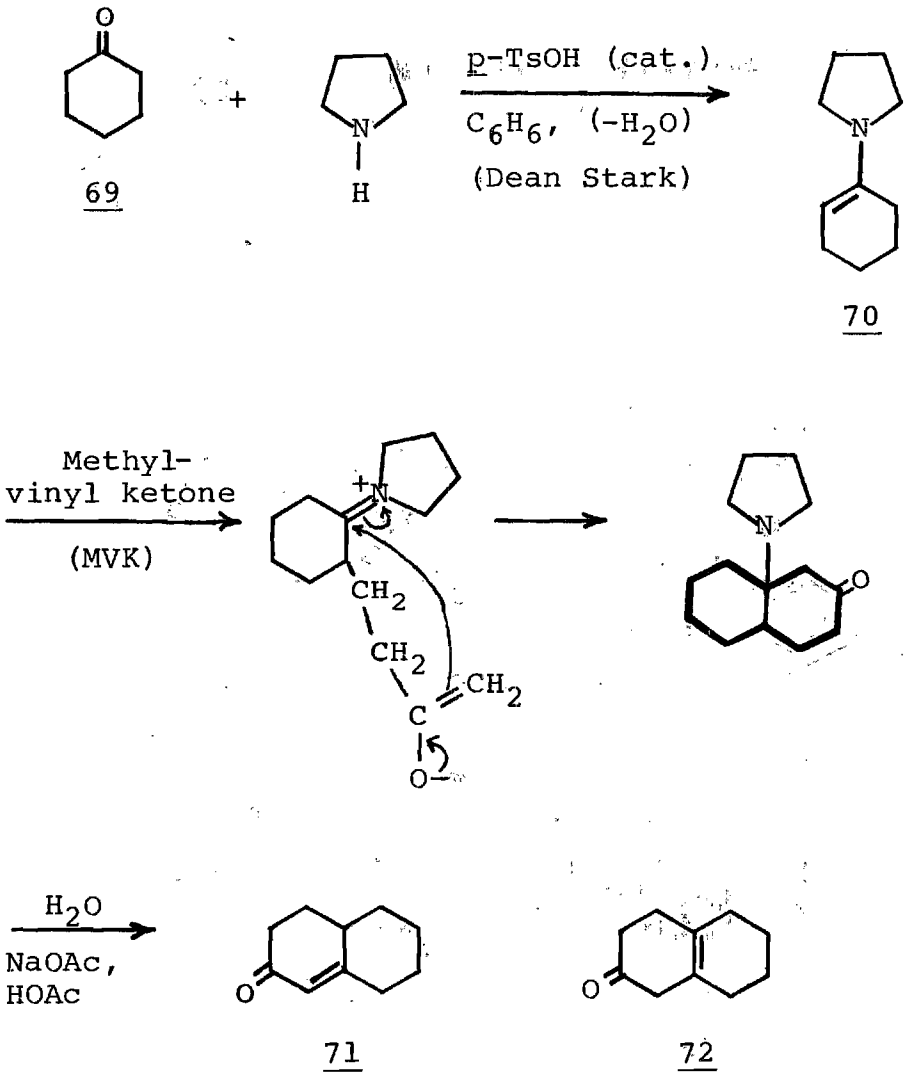


Figure 17. Scheme for the Preparation of $\Delta^{4(10)}$-Octalin-3-one 71 and 9-Methyl-$\Delta^{4(10)}$-octalin-3-one 75.

Nitrile Syntheses

Reactions of "Naked" Cyanide with Organic Substrates under Liquid-Liquid Phase-Transfer Catalytic Conditions

Although a variety of synthetic methods have been developed for organic nitriles,[89-91,93,96,191,214-227] simple displacement and addition reactions by cyanide ion are the most often used.

The reactions of "naked" anions so far reported in this thesis were carried out under solid-liquid phase-transfer catalytic (heterogeneous) conditions with the 18-crown-6 acting as the phase-transfer catalyst. We have also investigated the reactions of "naked" anions with organic substrates in liquid-liquid phase-transfer catalytic conditions. The reactions of "naked" cyanide and of "naked" acetate with both primary and secondary octyl halides have been investigated. The reactions were carried out using the pure organic substrate as the organic phase and a water solution of KCN or KOAc as the aqueous phase both in the presence and in the absence of 18-crown-6. The potassium salt was either completely or partially dissolved in water. These experiments are to be contrasted to those of Starks et al.[89-91] who used quaternary ammonium or quaternary phosphonium salts as liquid-liquid phase-transfer catalysts (Figure 3) and those of Liotta et al.[94-96] who used crown ether as a solid-liquid phase transfer catalyst (Figure 4).

The results for the nitrile syntheses are summarized in Table 8. High yields of products were obtained under relatively mild conditions. The reactions were carried out by simply pouring a substrate over excess, aqueous KCN or KOAc (the salts being partially or completely dissolved in water) and about 1.0 mole percent of 18-crown-6. The resulting two-phase system was stirred vigorously at reflux temperature until conversion was complete. Little or no reaction was found to take place in the absence of crown under the same conditions covering the same periods of time.

At primary and secondary positions, the bromides were displaced more rapidly than the chlorides in all cases; however, less alkene and a higher overall yield of substitution product was obtained with the chlorides. In this regard, bromide was shown to be displaced by the cyanide ion more rapidly than chloride in ethanol-water, e.g., ethylene dibromide was smoothly converted to succinonitrile, but ethylene dichloride was found to be unreactive.[214] This also compares well with other methods where the bromides were shown to be displaced more rapidly than the chlorides except for the results reported by Liotta, Cook, and Bowers.[96] The latter authors reported the primary chlorides to react much faster than the corresponding bromides under the reaction conditions (Appendix 3). For example, benzylchloride reacted over 100 times faster than benzyl bromide in a comparison of $t_{\frac{1}{2}}$.

Table 8. Reactions of Potassium Cyanide[a] with Organic Substrates in the Presence and in the Absence of 18-Crown-6 under Liquid-Liquid Phase-Transfer Catalysis.

Substrate	Run	Salt	Substrate Conc. Mole %[b] (Molarity)	Crown Conc. Mole % (Molarity)	Solvent (Mole %)[c]	Nature of Reaction	Temp. °C	$t_{\frac{1}{2}}$[d] Hour	t_{end}[e] Hour	Product[f] (Yield)
1-Chloro-octane	1	KCN[g]	14.69 (5.45M)	0.72 (0.27M)	H_2O (40.50)	A[h]	110	4.5	13.5	1-Cyanooctane (92.0)
1-Bromo-octane	2	KCN	13.70 (3.82M)	0.82 (0.28M)	H_2O (40.60)	A	110	0.6	0.75	1-Cyanooctane (93.2)
1-Chloro-octane	3	KCN	12.42 (2.69M)	1.05 (0.31M)	H_2O (55.31)	B[i]	112	9.5	39.2	1-Cyanooctane (89.9)
1-Bromo-octane	4	KCN	13.42 (4.42M)	1.18 (0.38M)	H_2O (52.20)	B	110	0.9	02.2	1-Cyanooctane (91.5)
1-Chloro-octane	5	KCN	14.70 (5.02M)	0.00 (0.00M)	H_2O (38.60)	A	110	---	----	Refluxed 100hr No Reaction
1-Bromo-octane	6	KCN	13.80 (4.38M)	0.00 (0.00M)	H_2O (40.90)	A	106-108	22	50.0	1-Cyanooctane (82.0)
2-Chloro-octane	7	KCN	16.20 (5.83M)	1.21 (0.43M)	H_2O (33.92)	A	114	53	768	2-Cyanooctane (58.6) Octenes (1.6)[j]
2-Bromo-octane	8	KCN	15.34 (4.77M)	1.10 (0.35M)	H_2O (32.87)	A	117	4.17	08.0	1-Cyanooctane (86.2) Octenes (4.1)

Table 8 (Continued)

Substrate	Run	Salt	Substrate Conc. Mole %[b] (Molarity)	Crown Conc. Mole %[b] (Molarity)	Solvent (Mole %)[c]	Nature of Reaction	Temp °C	$t_{1/2}$[d] Hour	t_{end}[e] Hour	Product (Yield)
2-Chloro-octane	9	KCN	13.60 (4.76M)	1.15 (0.34M)	H_2O (56.93)	B	108	56	_k	2-Cyanooctane (60.0)[L] 2-Chlorooctane (35.0)[L]
2-Bromo-octane	10	KCN	16.02 (2.47M)	1.12 (0.35M)	H_2O (67.40)	B	109	8.0	17.1	2-Cyanooctane (82.0) Octenes (6.1)
2-Chloro-octane	11	KCN	14.66 (3.92M)	0.00 (0.00M)	H_2O (41.57)	A	111	_m	_m	2-Chlorooctane (100)[n]
2-Bromo-octane	12	KCN	15.55 (4.77M)	0.00 (0.00M)	H_2O (33.24)	A	110	_m	_m	2-Bromooctane (100)

[a]All reactions included in this Table were carried out under liquid-liquid phase-transfer catalytic (heterogeneous) conditions.
[b]The concentration of substrate and crown are reported as mole percent and molarity.
[c]Water concentration is reported as mole percent. The use of water in these reactions eliminates anhydrous conditions and makes the reactions easier to handle and carry out.
[d]$t_{1/2}$ is defined as the time required for 50% of the starting material to react.
[e]Estimated as closely as possible.
[f]Isolated yields. For most reactions, glc and nmr analysis showed a quantitative conversion to products.
[g]2-3 folds excess of salt was used.
[h]Saturated solution of the salt was used.

Table 8 (Continued)

[i] Unsaturated solution of the salt was used.

[j] The low temperature chromatogram (3% SE 30, 5' x 1/4", 35°C) of the olefin mixture overlapped in appearance and $t_{retention}$ that of an isolated and characterized mixture of 1-octene and cis- and trans-2-octene (supplied by H. P. Harris)[182]. Nmr spectra (CH_3CN, external TMS) showed a broad multiplet containing 5 distinct peaks at δ5.20 that overlapped with the proton band of the isolated octene mixture.

[k] $t_{1/2}$ for this reaction was estimated to be 56 hr. Reaction was stopped after 100 hr and glc analysis showed the presence of 30% of unreacted starting material.

[l] In cases where reactions were not complete even after prolonged times, the reaction was usually stopped and analysis of reaction products and starting material was based on glc analysis and percent of each was found from peak areas.

[m] Less than 5% reaction occurred after refluxing for 42 hr.

[n] The reaction was stopped after 100 hr. Percentages based on glc analysis of reaction mixture. No attempt was made to isolate the products.

This observation was contrary to the normally-accepted leaving group order,[114] and was also contrary to what had been reported for all but one of the other cyanide systems reported by Brandstrom, who found opposite rate results with cyanide ion in liquid poly (ethylene-glycols).[89g] Brandstrom attributed the reversal in rate in the poly (ethylene glycol)-cyanide system to the heterogeneous character of the reaction, with relative solubilities of the salts considered important to the rate.[89g]

With primary substrates, no elimination products were found and the yields were essentially quantitative (Table 8, Runs 1-6), whereas with secondary substrate reactions, a small percentage of alkenes and a high yield of substitution products were obtained (Table 8, Runs 7-12). Moreover, reactions involving unsaturated salt solutions were much slower than the reactions involving saturated ones (Table 8, Runs 3, 4, 9, and 10 versus 1, 2, 11, and 12, respectively). Difficulty was encountered in driving the reactions to completion especially in reactions where the 2-chlorooctane was the substrate. The difficulty may have originated from complexation of the crown ether with the eliminated acid, as Schori and Jagur-Grodzinski have observed complexation of crown ethers with HBr in solution.[36] Such complexation would decrease the concentration of free 18-crown-6, and hence slow the rate of reaction. HBr eliminates more readily than HCl,

and therefore a higher yield of substitution product with the secondary alkyl bromide was expected. The octenes resulting from elimination reactions on secondary substrates reported in Table 9, Runs 7, 8, and 10, consisted of a mixture of 1-octene and cis-,trans-2-octenes by low temperature comparison with a known mixture.[182]

An important conclusion that could be drawn from the reactions of "naked" cyanide with 1^{o} and 2^{o} octyl halides is that compared to earlier cyanation methods (for a literature survey of earlier cyanation methods, refer to Appendicies 3, 8, and 17-21), the "naked" cyanide procedure appears to be superior to the ethanol-water method in reaction time, simplicity of work up, and yield. It also compares favorably to the dipolar, aprotic solvent and phase-transfer catalyst (PTC) systems in both reaction time and yield for converting 1^{o} halides to nitriles, while affording lower reaction temperatures and improved simplicity of work up. For 2^{o} substrates, comparable yields to those presented in Appendicies 3, 8, 12, and 13 were obtained in much shorter times for the DMSO and PTC systems, although reaction temperatures were higher.

Acetate Syntheses

Liotta and Harris,[95] utilizing nmr techniques, reported enhanced solubility of KOAc (by a factor of 200) in the presence of 0.14M 18-crown-6 solution at 25°C (Table 5). Utilizing flame photometry, we have measured the solubilities of a variety of common potassium salts in acetonitrile at 25°C both in the presence and in the absence of 18-crown-6 and have confirmed this enhanced KOAc solubility caused by the addition of 18-crown-6 (by a factor of 204).

Reactions of "Naked" Acetate with 2-Chloro-4-methylcyclohexanone

The use of "naked" acetate in promoting dehydrohalogenation and/or substitution of a mixture of cis- and trans-2-chloro-4-methylcyclohexanone resulted in a facile substitution at the secondary carbon position. Thus, stirring a mixture of cis- and trans-2-chloro-4-methylcyclohexanone (a ratio of 1.4 of cis to trans) with "naked" acetate in acetonitrile solution proceeded very slowly at room temperature. At reflux temperature, however, the reaction proceeded smoothly to simple displacement products, cis-2-acetoxy-4-methylcyclohexanone (96% by glpc), 2% of the trans-acetate product and 2% alkenes (Reaction 53). It is interesting to note that no "Favorskii rearrangement products" were obtained in this latter case even though the reaction was heated under reflux for seven hours. Moreover, little or no reaction was found to take place in the absence of crown under the same conditions covering the same periods of time.

In this regard, Liotta and Harris[95] have reported the reaction of 2-chloro-2-methylcyclohexanone (Run 7, Appendix 2) with "naked" acetates in acetonitrile at reflux temperature to yield a mixture of acetates with only 10% 2-methylcyclohexenone (Reaction 14). From these two reactions (14 and 53), it can be shown that the "naked" acetate reagent is a potent nucleophile. Moreover, reaction 53 was much faster, cleaner, and produced higher yields than the ethanol-water method used earlier to prepare 2-acetoxy-4-methylcyclohexanone.[164]

Reaction of "Naked" Acetate with Organic Substrates under Liquid-Liquid Phase-Transfer Catalytic Conditions

The reactions reported in Table 9 were carried out under exactly the same conditions as those reported for the reactions of "naked" cyanide with organic substrates under liquid-liquid phase-transfer catalytic conditions (Table 8). The following conclusions could be drawn from the reactions of "naked" acetate with primary and secondary octyl halides: as shown in Table 9, the displacement reactions performed with potassium acetate solubilized in substrate-water mixtures proceeded smoothly and mildly to high yields of products. The reactions were carried out by simply pouring a substrate over excess, aqueous KOAc (solution being unsaturated or saturated in salt), and about 1.0 mole percent 18-crown-6. The resulting two-phase system was stirred vigorously at reflux temperature until conversion was complete. Little or no reaction was

Table 9. Reactions of Potassium Acetate with Organic Substrates in the Presence and Absence of 18-Crown-6 under Liquid-Liquid Phase-Transfer Catalysis.[a]

Substrate	Run	Salt	Substrate Conc. Mole %[b] (Molarity)	Crown Conc. Mole %[b] (Molarity)	Solvent (Mole %)[c]	Nature of Reaction Mixture	Temp °C	$t_{\frac{1}{2}}$[d] Hour	t_{end}[e] Hours	Product (Yield)[f]
1-Chloro-octane	1	KOAc[g]	16.18 (5.26M)	1.29 (0.42M)	H_2O (36.71)	A[h]	112	3.2	10	1-Acetoxyoctane (96.4)
1-Bromo-octane	2	KOAc	15.92 (4.68M)	1.26 (0.36M)	H_2O (34.64)	A	110	0.67	1.5	1-Acetoxyoctane (94.2)
1-Chloro-octane	3	KOAc	12.69 (4.60M)	1.14 (0.38M)	H_2O (54.62)	B[i]	112	7.80	28.2	1-Acetoxyoctane (92.3)
1-Bromo-octane	4	KOAc	12.69 (3.98M)	1.14 (0.32M)	H_2O (54.62)	B	110	1.28	3.00	1-Acetoxyoctane (96.7)
1-Chloro-octane	5	KOAc	16.32 (5.03M)	0.00 (0.00M)	H_2O (36.72)	A	114-118	73	204	1-Acetoxyoctane (76.1)
1-Bromo-octane	6	KOAc	16.02 (4.72M)	0.00 (0.00M)	H_2O (37.23)	A	110	22	75	1-Acetoxyoctane (80.0)
2-Chloro-octane	7	KOAc	16.51 (5.69M)	1.26 (0.41M)	H_2O (36.70)	A	115	68	_j	2-Acetoxyoctane (50.0) 2-Chlorooctane (40.0) Octenes (10.0)[k]

Table 9 (Continued)

Substrate	Run	Salt	Substrate Conc. Mole %[b] (Molarity)	Crown Conc. Mole %[b] (Molarity)	Solvent (Mole %)[c]	Nature of Reaction Mixture	Temp °C	$t_{\frac{1}{2}}$[d] Hour	t_{end}[e] Hours	Product (Yield)[f]
2-Bromo-octane	8	KOAc	16.04 (5.60M)	1.29 (0.45M)	H_2O (35.32)	A	116	0.92	2.67	2-Acetoxyoctane (72.6) Octenes (15.9)
2-Chloro-octane	9	KOAc	14.57 (4.97M)	1.12 (0.35M)	H_2O (53.60)	B	114	90.0	---	---[e]
2-Bromo-octane	10	KOAc	14.57 (4.18M)	1.12 (0.29M)	H_2O (53.60)	B	111	2.50	11.6	2-Acetoxyoctane (69.5) Octenes (14.1)
2-Chloro-octane	11	KOAc	16.51 (4.78M)	0.00 (0.00M)	H_2O (36.60)	A	116	---	---	---[m]
2-Bromo-octane	12	KOAc	16.37 (4.76M)	0.00 (0.00M)	H_2O (35.09)	120	120	---	---[n]	2-Bromooctane (54.3) 2-Acetoxyoctane (30.5) Octenes (15.2)

[a]All reactions included in this Table were carried out under liquid-liquid phase-transfer catalytic (heterogeneous) conditions.
[b]The concentration of substrate and crown are reported as mole percent and molarity.
[c]Water concentration is reported as mole percent. The use of water in these reactions eliminates anhydrous conditions as makes the reactions easier to handle and carry out.

Table 9 (Continued)

[d] $t_{1/2}$ is defined as the time required for 50% of the starting material to react.
[e] Estimated as closely as possible.
[f] Isolated yields, except for runs 7 and 12 where numbers in brackets refer to glc analysis. For most reactions, glc and nmr analysis showed a quantitative conversion to products.
[g] 2-3 folds excess of salt was used.
[h] Saturated solution of the salt was used.
[i] Unsaturated solution of the salt was used.
[j] $t_{1/2}$ for this reaction was estimated to be 68 hr. Reaction was stopped after 110 hr. and glc analysis showed the presence of 40% of unreacted starting material.
[k] The low-temperature chrometogram (3% SE 30, 5' x 1/4", 35°C) of the olefin mixture overlapped in appearance and $t_{retention}$ that of an isolated and characterized mixture of 1-octene and cis- and trans-2-octene (by H. P. Harris). Nmr spectra (CH_3CN, external TMS) showed a broad multiplet containing 5 distinct peaks at δ5.20 that overlapped with the proton band of the isolated octene mixture.
[l] Reaction was stopped after refluxing for 97 hr. No attempt was made to isolate any products.
[m] Less than 5% reaction occurred after refluxing for 100 hr.
[n] Reaction was stopped after refluxing for 115 hr. No attempt was made to isolate any products.

found to take place in the absence of crown under the same conditions covering the same periods of time. Using the glc monitoring procedure as was used for the reactions with KCN earlier, it was found that the reactions at primary positions were essentially quantitative (Runs 1-6, Table 9). The reactions at secondary positions were better than 98% complete as shown by glc analysis (Runs 7, 8, 10, and 12, Table 9). At primary and secondary positions, the bromides were displaced more rapidly than the chlorides in all cases; (compare Runs 1, 3, 5, 7, 9, and 11 with Runs 2, 4, 6, 8, 10, and 12, respectively, Table 9) however, less alkene and a higher overall yield of substitution product was obtained with the chloride. With primary substrates, no elimination products were found and the yields were essentially quantitative (Runs 1-6, Table 9). With secondary substrate reactions, a small percentage of alkenes and a high yield of substitution products were obtained (Runs 7-12, Table 9). Moreover, reactions which involved unsaturated salt solutions were much slower than the reactions which involved saturated ones. Also, difficulty was encountered in driving the reactions to completion, especially in reactions where the 2-chlorooctane was the substrate. The difficulty could be explained as originating from complexation of the crown ether with the eliminated acid. The octenes resulting from elimination reactions on secondary substrates reported in Table 9, Runs

7, 8, 10, and 12 consisted of a mixture of 1-octene and cis- and trans-2-octenes.

Most of the nucleophilic displacements on primary and secondary octyl halides were carried out by potassium cyanide (Appendicies 3, 15, and 17-21),[96] fluoride (Appendix 1),[94] bromide[93] and iodide[93] (Reaction 38), and acetate (Appendix 2).[95] The poor nucleophilicity of the acetate ion toward various substrates in condensed systems has been attributed to a combination of polarizability, basicity, and solvation factors. Thus, nucleophilic displacements by the acetate ion or "naked" acetate have not been studied extensively on primary and secondary octyl halides except for the study undertaken by Liotta and Harris[95] (Appendix 2) where they utilized 18-crown-6 under solid-liquid phase-transfer conditions. Here we report the reactions (Table 9) under liquid-liquid phase-transfer catalytic conditions. The reaction times reported and the product yields are comparable to yields obtained by other synthetic methods utilizing the same or different salts.

CHAPTER IV

CONCLUSIONS

In this thesis has been reported the solubilities of a variety of common potassium salts in acetonitrile at 25°C in the presence and in the absence of 18-crown-6 (catalytic, 0.15M). The solubility enhancement, caused by the presence of 18-crown-6, is quite dramatic for KCl (228), for KOAc (204), and for KCN (108). The solubility enhancement is moderate for KBr (64) and KN_3 (57), and marginal for KF (14), KI (2), and KSCN (1.13). It should be noted that KI and KSCN have high inherent solubilities in pure acetonitrile.

Facile exclusive elimination, substitution, and rearrangement reactions were effected by "naked" anions on 2-chloro-2-mehtylcyclohexane 34, a substrate subject to "Favorskii rearrangement products". The use of "naked" halides in promoting dehydrohalogenation of 34 in benzene and acetonitrile solvents, respectively, showed the "naked" bromide in acetonitrile solvent to be the most effective dehydrohalogenating agent among the naked halides (exclusive elimination, 66% isolated yield). This proved the "naked" bromide to be a potent base. "Naked" fluoride gave elimination product (2-methylcyclohexenone, 36% isolated yield), and substitution product (2-fluoro-2-methylcyclohexanone, 26% isolated yield). This proved the "naked" fluoride to be a

potent base and a potent nucleophile. "Naked" chloride gave exclusively the elimination product 2-methylcyclohexenone in 50% yield. With "naked" chloride in benzene solvent and "naked" iodide in acetonitrile solvent, respectively, less than 5% reaction (elimination and substitution) was observed. Likewise, ambient temperatures or identical systems without 18-crown-6 resulted in drastically reduced rates of reaction (less than 5%). In all cases, crown was present in catalytic concentrations indicating that it behaved as a phase-transfer catalyst in solid-liquid phase-transfer catalytic conditions.

"Naked" cyanide was found to be a potent nucleophile in displacement reactions at sterically hindered positions on substrates subject to "Favorskii rearrangements". The reaction of "naked" cyanide with 34 resulted in an exclusively facile substitution at the tertiary carbon center. At room temperature a quantitative conversion to the simple displacement product, 2-cyano-2-methylcyclohexanone 35, was obtained thus providing a potentially useful procedure for introducing a carbon functional group at a rather sterically hindered position. The reaction proceeded at a much faster rate in acetonitrile than in benzene. Excellent yields of products were obtained in the absence of crown in acetonitrile but reaction times were quite long. At reflux temperature, the "Favorskii rearrangement product" cyclopentane carbonylcyanide,1-methyl 36, was obtained in high yield.

Studies on the mechanisms of the above two reactions have indicated the substitution reaction to occur most probably *via* S_N2 displacement followed by equilibration while the rearrangement reaction occurred *via* the "benzilic acid" rearrangement mechanism.

Reaction of "naked" cyanide with *cis*-2-chloro-4-methylcyclohexanone 51 also proceeded smoothly to produce the simple displacement product *cis*-2-cyano-4-methylcyclohexanone 54. Reaction of "naked" acetate with a mixture of *cis*- and *trans*-2-chloro-4-methylcyclohexanone 51 also proceeded smoothly to produce the simple displacement product *cis*-2-acetoxy-4-methylcyclohexanone 63. In both reactions, good isolated yields of displacement products were obtained, and, little or no reaction was found to take place in the absence of crown under the same conditions covering the same periods of time.

The versatility of the "naked" cyanide reagent in Michael type addition reactions to conjugated α,β-unsaturated ketones was demonstrated in the smooth and stereoselective hydrocyanation of Δ^4-cholesten-3-one in the presence of acetone cyanohydrin. No reaction was observed in the absence of crown, acetone cyanohydrin, and KCN. Excellent yields of hydrocyanation products were obtained in benzene and acetonitrile and no cyanide hydrolysis products or dimers were detected. The lower the temperature the greater was the preference for formation of the β-isomer. At ambient

temperatures an α/β ratio of 1/10 was obtained in benzene. These stereochemical results appeared to be equal to or superior to the results obtained with other hydrocyanating reagents. Hence, the potential synthetic value of the mild and facile stereospecific route is apparent.

Finally, the reactions of "naked" cyanide and "naked" acetate, respectively, with primary and secondary octyl halides were studied. The reactions described in this thesis in this regard were carried out in the presence and absence of catalytic concentrations of 18-crown-6 using aqueous KCN or KOAc. The following conclusions could be drawn from the data:

(i) At 1^{o} and 2^{o} positions, the bromides were displaced more rapidly than the chlorides in all cases; (ii) with 1^{o} substrate reactions, no elimination products were found and the yields were essentially quantitative; (iii) with secondary substrate reactions, a small percentage of alkenes and a high yield of substitution products were obtained, the conversions being essentially quantitative; (iv) in all cases, crown was present in catalytic quantities, indicating that it behaved as a phase-transfer catalyst; (v) little or no reaction was found to take place in the absence of 18-crown-6 under the same conditions covering the same periods of time; and (vi) reaction times were shorter and the product yields were also comparable to yields obtained by other synthetic methods.

An important conclusion that could be drawn from the reactions of "naked" cyanide with 1^{o} and 2^{o} octylhalides is that compared to earlier cyanation methods (Appendices 17 and 21), the "naked" cyanide procedure appears to be superior to the ethanol-water method in reaction time, simplicity of work up, and yield. It also compares favorably to the dipolar, aprotic solvent and phase-transfer catalyst (PTC) systems in both reaction time and yield for converting 1^{o} halides to nitriles, while affording lower reaction temperatures and improved simplicity of work up. For 2^{o} substrates, comparable yields to those of previous workers were obtained in much shorter times for the DMSO and PTC systems, although reaction temperatures were higher.

Due to the poor nucleophilicity of acetate ion toward various substrates in condensed systems, the reactions of potassium acetate with organic substrates in the presence and absence of 18-crown-6 under liquid-liquid phase-transfer catalysis represent synthetically useful new routes for preparing n-octyl acetates in quantitative to fair yields and secondary octyl acetates in good isolated yields of products.

CHAPTER V

RECOMMENDATIONS

The preparation of several "naked" anions and their utilization in substitution, addition, elimination, and rearrangement reactions with a wide variety of organic substrates have proved "naked" anions to be useful reagents to the synthetic organic chemist.

Facile elimination, substitution, addition, and rearrangement reactions affected by "naked" anions should be further explored. The reactions of "naked" anions with 2-chloro-4-methylcyclohexanone 51 (an α-haloketone and a substrate subject to "Favorskii rearrangement products") should be further investigated. The reactions of "naked" cyanide and "naked" acetate with cis-51 have already been shown to give exclusive facile substitution reactions. The use of other "naked" anions (e.g., N_3^-, F^-, Cl^-, Br^-, SCN^-, OMe^-, OH^-, and PhO^-) in promoting elimination and/or substitution on 51 should prove interesting. It would also be interesting to study the effect of temperature on the reaction of "naked" cyanide with 51 and with 2-cyano-4-methylcyclohexanone 54 to see if any "Favorskii rearrangement products" are observed as is the case with 2-chloro-2-methylcyclohexanone 34 and its simple cyanide displacement product 35 in their reactions with "naked" cyanide anion under reflux temperature.

Metal alykens have been reported to undergo 1,2-additions across the carbonyl carbon of ketones to give ethynyl compounds. The reactions of 51 and 54, respectively with metal alkenes $RC\equiv\bar{C}\overset{+}{M}$ (where $R^- = H^-$, CH_3^-, $HC\equiv C^-$, etc., and $M^+ = Li^+$ or K^+) in the presence and in the absence of crown ethers (12-crown-4 used with Li^+ and 18-crown-6 used with K^+) in tetrahydrofuran at low temperatures should prove interesting, especially if exclusive facile nucleophilic substitution occurs regardless of steric hindrance of the substrate or of the incoming groups.

The newly developed hydrocyanation method using "naked" cyanide and acetone cyanohydrin should be expanded to other complicated natural products and/or derivatives as well as to simpler conjugated α,β-unsaturated ketones as 2-cyclohexenone, $\Delta^{4(10)}$-octalin-3-one 71 and 9-methyl- $\Delta^{4(10)}$-octalin-3-one 75.

The use of "naked" acetate both as nucleophile and as base in liquid-liquid phase-transfer catalytic heterogeneous reactions should be further explored.

Solvent effects, with "naked" cyanide, "naked" acetate, and "naked" halides in other more polar aprotic solvents such as DMSO, DMF, or HMPA should be studied. Studies are also needed to find ways to drive the reactions (especially those of "naked" cyanide and "naked" acetate with secondary octyl halides reported in Appendices 16 and 22) to completion.

Appendix 1. Reactions of "Naked" Fluoride with Organic Substrates.

	Substrate	Solvent	Products[a]	Concentrations (M) Crown	Substrate	Temp °C	t1/2 Hour[b]
1.	Benzyl Bromide	CH_3CN	Benzyl Fluoride	0.19	2.00	83	11.50
2.	1-Bromooctane	CH_3CN	1-Fluorooctane (92%) 1-Octene (8%)	0.19	1.16	83	115.00
		C_6H_6	1-Fluorooctane (92%) 1-Octene (8%)	0.68	2.90	90	128.00
3.	2-Bromooctane	C_6H_6	2-Fluorooctane (32%) 1- and 2-Octene (68%)	0.50	2.80	90	240.00
4.	Bromocyclohexane	CH_3CN	Cyclohexene	0.15	3.61	83	104.00
5.	2-Chloro-2-methyl-cyclohexanone	CH_3CN	2-Fluoro-2-methylcyclohexanone (31%) 2-Methyl-2-cyclohexenone (69%)	0.15	3.30	83	20.00
6.	2,4-Dinitrochlorobenzene	CH_3CN	2,4-Dinitrofluorobenzene			25	5.00
						83	0.12
7.	Acetyl Chloride	CH_3CN	Acetyl Fluoride	0.14	7.00	25	5.50

[a] In all cases conversion to products was quantitative. All spectral data (nmr, ir and mass spectra) of the isolated products were consistent with the assigned structures.

[b] The time for one-half conversion of starting materials to products is tabulated as an approximate indication of the relative rates of reaction.

Appendix 2. Reactions of "Naked" Acetate with Organic Substrates.[a]

	Substrate	Products[b]	Concentrations (M) Crown	Concentrations (M) Substrate	Temp °C	Time (Hours)
1.	Benzyl Bromide	Benzyl Acetate (100%)	0.16	3.40	25	2
2.	n-$C_6H_{13}Br$	n-$C_6H_{13}OAc$ (100%)	0.10	1.40	25	150
3.	n-$C_8H_{17}Br$	n-$C_8H_{17}OAc$ (96%)	0.10	1.40	83	3
4.	1,2-Dibromoethane	Ethylene diacetate (90%)	0.09	1.30	83	3
5.	1,2-Dibromoethane[c]	Ethylene diacetate (23%) 2-Bromoethyl acetate (77%)	0.06	1.90	83	3
6.	2-Bromooctane	2-Acetoxyoctane (ca. 90%) Octenes (ca. 10%)	0.10	1.40	83	20
7.	2-Chloro-2-methyl-cyclohexanone[d]	2-Methylcyclohexenone (ca. 10%) cis-2-acetoxy-6-methylcyclo-hexanone (ca. 54%) trans-2-acetoxy-6-methylcyclo-hexanone (ca. 10%) 2-acetoxy-2-methylcyclohexanone (ca. 25%)	0.15	2.90	83	1

[a]All reactions were run using at least a two-fold excess of potassium acetate.
[b]All products show ir, nmr and mass spectra consistent with the proposed structures.
[c]Equimolar quantities of 1,2-dibromoethane and potassium were used in this experiment.
[d]The product acetates were assigned structures based on evidence from a known mixture prepared by the method of H. O. House and F. A. Richey, J. Org. Chem., 34, 1430 (1969).

Appendix 3. Reactions of "Naked" Cyanide with Organic Substrates.

Substrate	Run	Solvent	Products (Yield %)	Concentrations M[b] Crown	Substrate	Temp °C	t1/2[c] Hour	t_{end} Hour
1,3-Dibromopropane	1	CH_3CN	Glutaronitrile (97.3)[d]	0.151	1.80	83	7.0	25.0
	2	CH_3CN	Glutaronitrile (94.9)[d]	0.147	1.80	Ambn't	10.5	48.0
	3	C_6H_6	Glutaronitrile (100)[e]	0.147	1.80	90	12.0	40.0
	4	C_6H_6	Glutaronitrile (100)[e]	0.147	1.80	Ambn't	10.0	49.0
1-Bromo-3-chloro-propane	5	CH_3CN	Glutaronitrile (100)[e]	0.152	1.80	83	1.1	30.0
1,3-Dichloropropane	6	CH_3CN	Glutaronitrile (96.8)[d]	0.154	1.80	83	0.23	1.5
1,4-Dibromobutane	7	CH_3CN	Adiponitrile (100)[e]	0.141	1.80	83	6.5	14.5
	8	CH_3CN	Adiponitrile (100)[e]	0.141	1.80	Ambn't	11.0	57.0
1,4-Dichlorobutane	9	CH_3CN	Adiponitrile (94.7)[d]	0.144	1.80	83	0.2	0.7
	10	CH_3CN	Adiponitrile (86)[d]	0.144	1.80	Ambn't	8.0	75.0

Appendix 3 (Continued)

Substrate	Run	Solvent	Products (Yield %)	Concentrations M[b] Crown	Substrate	Temp °C	t1/2[c] Hour	t_{end} Hour
1-Bromohexane	11	CH_3CN	1-Cyanohexane (100)[e]	0.138	1.80	83	10.0	40.0
1-Chlorohexane	12	CH_3CN	1-Cyanohexane (90.6)[d]	0.139	1.80	83	0.5	2.2
2-Bromobutane	13	CH_3CN	2-Cyanobutane (69.7)[e]	0.141	2.00	83	16.0	32.0
	14	C_6H_6	2-Cyanobutane (43.4)[e]	0.140	2.01	90	58.0	66.0[f]
2-Bromooctane	15	CH_3CN	2-Cyanooctane (56)[d](62)[e] -Octene(17)[e,g]	0.119	2.00	83	14.0	78.0
2-Chloroctane	16	CH_3CN	2-Cyanooctane (77.5)[e,f] -Octene(3.1)[e,g,h]	0.122	2.00	83	59.0	244.0[h]
Cyclohexyl Bromide	17	CH_3CN	Cyclohexene (46)[e,f]	0.132	1.80	83		53.0[f]
Cyclohexyl Chloride	18	CH_3CN	Cyclohexene (32)[e,f]	0.146	1.80	83		122.5[f]
Benzyl Bromide	19	CH_3CN	Benzyl cyanide (100)[e]	0.146	1.80	Ambn't	13.0	25.0

Appendix 3 (Continued)

Substrate	Run	Solvent	Products (Yield %)	Concentrations M[b] Crown	Substrate	Temp °C	t1/2[c] Hour	t_{end} Hour
Benzyl Chloride	20	CH_3CN	Benzyl Cyanide (94.2)[d]	0.147	1.80	Ambn't	0.08	0.4
	21	CH_3CN	Benzyl Cyanide (20)[e,f]	0.000	1.80	Ambn't		75.0[f]
e-Dichlorobenzene	22	CH_3CN	No reaction[i]	0.145	1.80	83		109.0
Methacrylonitrile	23	CH_3CN	1,2-Dicyano-propane (91.9)[d,j]	0.132	1.51	83	0.30	0.6
(Acetone Cyano-hydrin)[f]	24	CH_3CN	1,2-Dicyano-propane (46)[e,f]		(1.78)			
				0.132	1.52	Ambn't		189.0[f]
	25	CH_3CN	1,2-Dicyano-propane (77)[d,k]	0.000	1.51	83	6.10	15.0

[a]For the isolated products, nmr, ir, and mass spectral data confirmed the pure compound's identity. Also, where possible, these spectra and glc data of the products were compared to those of the commercial compounds (runs 1-12).

[b]The reactions were run in a total of 25ml of solution, with a twofold excess of solid KCN per functional group for the substitution reactions, and a catalytic amount (approximately equivalent to 18-crown-6) of salt for the hydrocyanation.

[c]$t_{1/2}$ is defined as the time required for 50% of the starting material to react.

[d]Isolated yields. For these examples, glc and nmr analysis showed a quantitative conversion to the products.

[e]Calculated from glc and nmr data.
[f]In these runs, the reactions were stopped before completion.
[g]From glc analysis, 1-octene and both cis- and trans-2-octene were formed.
[h]There was difficulty in driving the reaction to completion. At 244 hr. the composition consisted of 7.4% starting material, 89.1% substitution product, and 3.5% olefin by glc analysis. The yields given in Appendix 1 are thus based on reacted starting material.
[i]The absence of reaction of "naked" cyanide with o-dichlorobenzene was in contrast to the results recently reported for the analogous KOH-CH_3OH-crown system in which a 40-50% yield of o-chloroanisole was obtained.[97]
[j]1.18 molar equivalent of acetone cyanohydrin was used. It functioned as a proton donor and a cyanide ion regenerator after initiation of the reaction by the "naked" cyanide.
[k]Run 25 was monitored frequently during the course of the reaction by glc, and thus a small quantity of product was lost in the transfers. The reaction was quantitative by glc and nmr analyses.

Appendix 4. Michael Condensations Initiated by Potassium Fluoride in the Presence and Absence of 18-Crown-6.

Product	Substrate Conc. (M)	Reactant Conc (M)	Crown Conc. (M)	Temperature[e] °C	Time Hour	% Yield Isolated	
γ-carbethoxy-γ-cyanopimelonitrile	1.0	1.1	0.098	Ambient	0.17	86	a
	1.0	1.1	0		4.00	80	a
	2.0	1.1	0.098	Ambient	0.25	83	a
	2.0	1.1	0	25°	43.00	84	a
	2.0	1.1	0.098	Ambient	0.25	90	a (dry CH_3CN)
γ,γ-dicarbethoxy-pimelonitrile	1.0	1.1	0.098	Ambient	4.00	73	b
	2.0	1.1	0.098	Ambient	3.50	82	b
ethyl α-carbethoxy-γ-cyanobutyrate	2.0	1.1	0	25°	121.00	84	b
diethyl γ-carbethoxy-γ-cyanopimelate	1.0	1.1	0.098	Ambient	3.00	64	c
	2.0	1.1	0.098	Ambient	0.17	75	c
	2.0	1.1	0	Ambient	13.00	67	c
diethyl α-carbethoxyglutarate	1.0	1.1	0.098	Ambient	3.00	62	d*
	2.0	1.1	0	25°	96.00	36	d
diethyl γ,γ-dicarbethoxy-pimelate	1.0	1.1	0.098	Ambient	3.00	8	d*
	2.0	1.1	0.098	Ambient	3.00	58	d

[a]Acrylonitrile as substrate with ethyl cyanoacetate as reactant.
[b]Acrylonitrile as substrate with diethyl malonate as reactant.
[c]Ethyl acrylate as substrate with ethyl cyanoacetate as reactant.
[d]Ethyl acrylate as substrate with diethyl malonate as reactant.
[d*]The same reaction.
[e]Ambient refers to a temperature increase above room temperature for a period of time during the reaction with eventual return to room temperature.

Appendix 5. Nucleophilic Substitutions in Octyl Derivatives Catalyzed by Dicyclohexyl 18-Crown-6[a] under Liquid-Liquid Phase-Transfer Conditions.[99]

Substrate	Reagent[b]	Temp. °C	Reaction Time Hr.	Yield %	Product n-$C_8H_{17}X$ (X =
1. n-$C_8H_{17}OSO_2Me$	KI	100	0.11	100	1
2. n-$C_8H_{17}OSO_2Me$	NaI	100	0.16	100	I
3. n-$C_8H_{17}OSO_2Me$	KBr	100	0.50	96	Br
4. n-$C_8H_{17}OSO_2Me$	NaBr	100	0.50	88	Br
5. n-$C_8H_{17}OSO_2Me$	KCl	100	3.00	89	Cl
6. n-$C_8H_{17}OSO_2Me$	NaCl	100	3.00	75	Cl
7. n-$C_8H_{17}OSO_2Me$	KF	100	42.00	65	F
8. n-$C_8H_{17}Br$	KI	100	1.50	92	I
9. n-$C_8H_{17}Br$	KI	80	3.00	100	I
10. n-$C_8H_{17}I$	KBr	80	3.00	40[d]	Br
11. n-$C_6H_{13}CH(OSO_2Me)Me$	KBr	100	2.50	67[e]	n-$C_6H_{13}CHBrMe$

[a] 0.05 molar equivalents.

[b] Saturated aqueous solution, 5 molar equivalents.

[c] The products were characterized by glc retention time.

[d] 60% of n-octyl iodide, same values after 26 hrs.

[e] 16% 2-octanol, 16% octenes, 1% 2-octyl mesylate.

Appendix 6. Addition Reactions Performed with "Naked" Cyanide in Conjunction with Acetone Cyanohydrin.

Substrate	Solvent	Concentration[a] Crown (M)	Substr. (M)	Temp °C	$t_{1/2}$ Hours	t_{end} Hours	Product	Yield % glc, nmr[c]	Yield % isolated[c]
Methacrylonitrile	CH_3CN	0.13	1.5	Reflux	0.3	0.6	1,2-Dicyano-propane	100	92
Acetone Cyanohydrin			1.8						
Methacrylonitrile	CH_3CN	0.13	1.5	Ambn't		189[d]	1,2-Dicyano-propane	46	--
Acetone Cyanohydrin			1.7						
Methacrylonitrile	CH_3CN	0.00	1.5	Reflux	6.0	15	1,2-Dicyano-propane	100	77[e]
Acetone Cyanohydrin			1.7						
Cyclohexanone	C_6H_6	0.13	1.6	Reflux		2.7	Cyclohexanone Cyanohydrin	100[f]	39
Acetone Cyanohydrin			1.4						(57)[g]
Cyclohexanone	C_6H_6	0.00	1.6	Reflux		3.0	Cyclohexanone	0	14
Acetone Cyanohydrin			1.8				Cyanohydrin		(70)[g]
Cyclohexanone	C_6H_6	0.13	1.5	Reflux		2.0	Cyclohexanone Cyanohydrin	100[f]	18
Acetone Cyanohydrin			1.7						

[a]The reactions were run in a total of 25ml of solution, with a 2-fold excess of solid KCN per functional group converted.

[b]The time required for 50% of the starting material to react was defined as $t_{\frac{1}{2}}$, and $t_{completion}$ was the time required for complete formation of the final product.

[c]The half-width band method was used to determine the glc yield for the hydrocyanations, with nmr showing only cyclohexanone cyanohydrin formed in the other reactions.

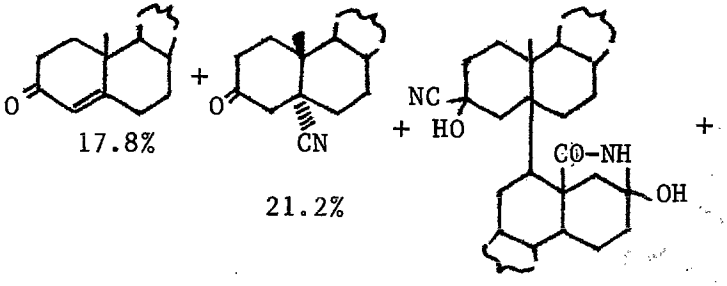
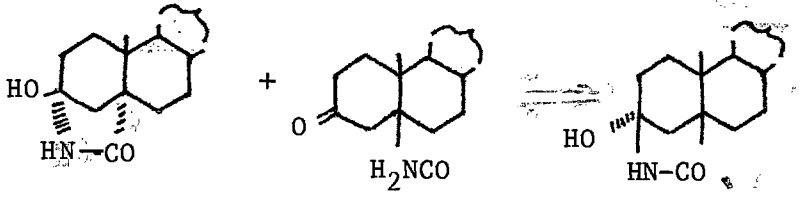
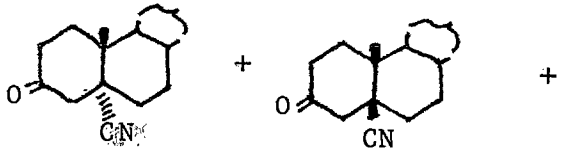
[d]This reaction was stopped before completion.

[e]The run was monitored frequently by glc, and thus a small quantity of 1,2-dicyanopropane was lost in the transfers.

[f]Nmr analyses of the crude reaction mixture showed complete conversion to cyclohexanone cyanohydrin.

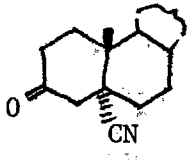
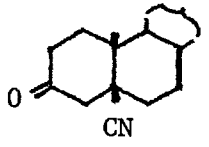
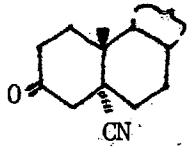
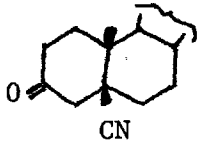
[g]The figure in parentheses is the yield of cyclohexanone isolated on distillation of the reaction mixture, indicating the extent of reversal of the unstable cyanohydrin.

Appendix 7. Comparison of Literature Methods for the Hydrocyanation of Δ^4-Cholesten-3-One 66.

Entry	Reference	Enone	Method and Conditions	Products [Yields %]
1[a]	205	66	Aq.KCN/MeOH, Reflux 6 hr.	 17.8% 21.2%  2.3%
2[b]	205	66	Aq.KCN/NH_4Cl/DMF Reflux at 100° 8 hr.	 40% 38%

+4% Mixed Fraction of 5α- and 5β- cyano-compounds
+2% α- and β-Lactams

Appendix 7. (Continued)

Entry	Reference	Enone	Method and Conditions	Products [Yields %]
3[c]	207a, b	66	DryCa(CN)$_2$/Dry N-Methyl-Pyrrolidone, Stir at 20°, 65 hr.	 +  + 40% 38% + 5% Mixed Fraction of 5α- and 5β-Cyano-compounds
4[d]	203	66	AlR$_3$/HCN (THF), r.t., 3.5 hr.	 +  49% 42%
5[e]	203	66	Et$_2$AlCN (THF) 15, 4 hr.	45% 42%
6[d,e]	203	66	Et$_2$AlCN (C_6H_6), r.t. 10 min.	40% 42%

Appendix 7. (Continued)

Entry	Reference	Enone	Method and Conditions	Products [Yields %]	
7[d,f]	203	66	i) $Et_2AlCN(C_6H_6)$, 25° 10hr. ii) Then equilibration at r.t. (Argon), 51 hr.	10%	90%

Advantages and/or Disadvantages of the Different Hydrocyanation Methods.

[a]Disadvantages: (i) The 5β-cyanochloestenone was more easily hydrolyzed than the 5α-epimer by the action of KCN as a strong base and yielded β-lactam.
(ii) Recovery of 17.8% of the starting enone.
(iii) Undesirable side products (∿32%) caused by hydrolysis and dimerization.

[b]Advantages: In order to avoid β-lactam (a side product in entry 1), cyanation of 66 was carried with 2.0 moles KCN and 1.5 moles NH_4Cl in DMF. As the excess NH_4OH which was produced by the consumption of cyanide anion, was liberated as ammonia by heating the reaction mixture was maintained at minimal basicity. Under these conditions a small amount of lactam was obtained and neither the starting material nor the dimer were obtained from the reaction mixture.

Disadvantages: (i) Lengthy work up involves converting the crude products to the tosylhydrazone and then cleaving the latter with pyruvic acid to get pure 5α- and 5β-isomers.
(ii) Procedure, however, was still found to be unsatisfactory both in efficiency and stereoselectivity in certain cases.

[c]This method gives a reasonably good yield of both 5α- and 5β-cyano compounds, but has two disadvantages: (i) undesirable side products, and (ii) when using wet $Ca(CN)_2$ and/or wet N-methylpyrrolidone a mixture of α- and β-lactams was produced.

Appendix 7.(Continued) Advantages and/or Disadvantages of the Different Hydrocyanation Methods.

[d]Advantages: (i) High efficiency (hydrocyanation of certain unreactive α-enones proved successful only with the new reagent).
(ii) High uniformity (the reaction is scarcely accompanied by undesirable side reactions).
(iii) High selectivity (other carbonyl functions are not usually affected by these reagents).
(iv) High stereoselectivity in the 1,4-adducts (the thermodynamically more stable or less stable stereoisomer can be preferentially prepared by applying either method (methods A and B in Nagata's papers refer to method and conditions used in entries 4 and 5, respectively).

Disadvantages: (i) Because of its reversible nature, the more efficient method B hydrocyanation does not go to completion in certain cases where the β-carbon of the enone system is electrically or sterically deactivated.

[e]Reaction is much faster in C_6H_6 than in THF (compare entries 5 and 6).

[f]While method A (entry 8) is irreversible and gives kinetically controlled products, method B (entries 5 and 7) is reversible and gives thermodynamically controlled products (trans/cis product ratio is decreased dramatically (entry 7) by prolongation of the reaction time and ultimately reaches an equilibrium ratio of 1/9 as shown in entry 7 (though ratio is obtained under somewhat vigorous reaction conditions).

Appendix 8. Reactions of 1-Chloro (or 1-Methylsulfate) Octane with Potassium Cyanide under Liquid-Liquid Phase-Transfer Catalytic Conditions.[217,218]

Substrate[a]	Reagent	Temperature °C	Time/Hour	Yield %	Product
$1\text{-}C_8H_{17}\text{-}Cl$	KCN	80	5	93	$1\text{-}C_8H_{17}\text{-}CN$
$1\text{-}C_8H_{17}\text{-}Cl$	KCN	80	5	94	$1\text{-}C_8H_{17}\text{-}CN$
$1\text{-}C_8H_{17}\text{-}OSO_2CH_3$	KCN	100	0.3	90	$1\text{-}C_8H_{17}CN$

[a]The reactions were carried out with a saturated aqueous solution of the reagent.

Appendix 9. Total Displacement of Primary Halides by "Naked" Cyanide.[180]

Substrate	Solvent	Concentration (M)[a] Crown	Substrate	Temp	Time/Hours $t_{1/2}$[b]	$t_{completion}$	Product	Yield (%) glc nmr[c]	isolated[c]
1-Chlorohexane	CH_3CN	0.14	1.8	Reflux	0.2	2.2	1-Cyano-hexane	100	91
1-Bromohexane	CH_3CN	0.14	1.8	Reflux	10	40	1-Cyano-hexane	100	--
Benzyl Chloride	CH_3CN	2.10	2.1	Ambn't	0.08	0.4	Benzyl Cyanide	100	94
Benzyl Chloride	CH_3CN	0.00	1.8	Ambn't	--	75[d]	Benzyl Cyanide	20	--
Benzyl Bromide	CH_3CN	0.15	1.8	Ambn't	13	25	Benzyl Cyanide	100	--
1,3-Dichloro-propane	CH_3CN	0.15	1.8	Reflux	0.2	1.5	1,3-Dicyano-propane	100	97[e]
1,3-Dichloro-propane	CH_3CN	0.15	1.8	Reflux	--	1.75	1,3-Dicyano-propane	100	92.5[e]
1,3-Dibromo-propane	CH_3CN	0.15	1.8	Reflux	7	25	1,3-Dicyano-propane	100	97
1,3-Dibromo-propane	CH_3CN	0.15	1.8	Ambn't	10.5	48	1,3-Dicyano-propane	100	97

Appendix 9 (Continued)

Substrate	Solvent	Concentration (M)[a] Crown	Substrate	Temp	Time/Hours $t_{1/2}$[b]	Time/Hours $t_{completion}$[b]	Product	Yield (%) glc nmr[c]	Yield (%) isolated[c]
1,3-Dibromo-propane	CH_3CN	0.15[f]	1.8	Reflux	--	25	1,3-Dicyano-propane	100	--
1,3-Dibromo-propane	C_6H_6	0.15	1.8	Ambn't	10	46	1,3-Dicyano-propane	100	--
1,3-Dibromo-propane	C_6H_6	0.15	1.8	Reflux	12	40	1,3-Dicyano-propane	100	--
1-Bromo-3-chloropropane	CH_3CN	0.15	1.8	Reflux	1	30	1,3-Dicyano-propane	100	--
1,4-Dichloro-butane	CH_3CN	0.14	1.8	Reflux	0.2	0.7	1,4-Dicyano-butane	100	95
1,4-Dichloro-butane	CH_3CN	0.14	1.8	Ambn't	8	75	1,4-Dicyano-butane	100	86
1,4-Dibromo-butane	CH_3CN	0.14	1.8	Reflux	6.5	14	1,4-Dicyano-butane	100	--
1,4-Dibromo-butane	CH_3CN	0.14	1.8	Ambn't	11	57	1,4-Dicyano-butane	100	--

[a]The reactions were run in a total of 25ml of solution with a 2-fold excess of solid KCN per functional group converted.
[b]The time required for 50% of the starting material to react was defined as $t_{1/2}$; $t_{completion}$ was the time required for complete formation of the final product.

[c]The half-width band method[228] was used to determine the glc yield, with isolated yields for representative cases instead of internal standards used to validate the accuracy of the glc procedure. Nmr spectra (where applicable) exhibited only peaks for the stated product.
[d]The reaction was halted before completion in this run.
[e]The first run (97%) included continuous extraction in the work-up, while in the second run (92.5%) hand-extraction techniques were utilized.
[f]Catalytic KCl (0.019 moles) was used in conjunction with 0.18 moles of KCN in this run.

Appendix 10. Products from the Incomplete Displacement of Primary Dihalides by "Naked" Cyanide.[180]

Substrate	Solvent	Concentration (M)[a] Crown	Substrate	Temp	Time/Hours $t_{1/2}$[b]	$t_{completion}$[c]	Products	Yield (%) glc nmr[d]	isolated[d]
1,3-Dichloro-propane	CH_3CN	0.15	1.8	Reflux	--	0.25	1-Chloro-3-cyanopropane	27	--
1,3-Dibromo-propane	CH_3CN	0.15	1.8	Reflux	7	7	1,3-Dicyano-propane	16.5	--
							1-Bromo-3-cyanopropane	33.0	--
1-Bromo-3-chloropropane	CH_3CN	0.15	1.8	Reflux	--	8	1,3-Dichloro-propane	--	7.5
							1-Bromo-3-chloropropane	--	11
							1,3-Dibromo-propane	--	23
							1-Halo-3-cyanopropane[e]	--	4.5-6.5
							1,3-Dicyano-propane	--	--
1,4-Dichloro-butane	CH_3CN	0.00	1.8	Reflux	25	45	1,4-Dicyano-butane	--	33
							1-Chloro-4-cyanobutane	--	30
1,4-Dibromo-butane	CH_3CN	0.14	1.8	Reflux	6.5	7.7	1,4-Dicyano-butane	--	26
							1-Bromo-4-cyanobutane	--	46

Appendix 10 (Continued)

Substrate	Solvent	Concentration (M)[a] Crown	Substrate	Temp	$t_{1/2}$[b]	$t_{completion}$[c]	Product	Yield (%) glc nmr[d]	Yield (%) isolated[d]
1,4-Dibromo butane	CH_3CN	0.0	1.8	Reflux	24	49	1,4-Dicyano-butane	87	--
							1-Bromo-4-cyanobutane	8	--

[a]The reactions were run in a total of 25ml of solution, with a 2-fold excess of solid KCN per functional group converted.

[b]The time required for 50% of the starting material to react was defined at $t_{1/2}$.

[c]The time of reaction when the incompleted process was stopped was designated as t_{stop}.

[d]The half-width band method[228] was used to determine the glc yield, with isolated yields for representative cases. Nmr spectra (where applicable) exhibited only peaks for the stated products.

[e]The relative percentages of isolated 1-bromo- and 1-chloro-3-cyanopropane in the mixture could not be ascertained from glc and nmr data.

Appendix 11. Representative Literature Preparations of Primary Nitrile Compounds.

Reagent	Refs.	Salts	Solv.	Conditions Temp. (°C)	Conditions Time (hr)	Products	Yield (%)
Benzyl Chloride	222	$C_6H_5\overset{+}{N}(CH_3)_3Cl^-$ (10%), NaCN	CH_2Cl_2, H_2O	95	0.2	Benzyl Cyanide	92
Benzyl Chloride	190	NaCN	EtOH, H_2O	100	4	Benzyl Cyanide	80-90
Benzyl Chloride	192	NaCN	DMSO	35-40	2.5	Benzyl Cyanide	92
Benzyl Chloride	226	Resin, CN Form	EtOH	65-75	3	Benzyl Cyanide	62
Benzyl Bromide	226	Resin, CN Form	C_6H_6	65-75	2	Benzyl Cyanide	72
1-Chlorooctane	89a	$C_{16}H_{33}\overset{+}{P}(Bu)_3Br^-$ (1%), NaCN	Reag., H_2O	105	3	1-Cyanooctane	95
1-Bromooctane	89a	$C_{16}H_{33}\overset{+}{P}(Bu)_3Br^-$ (1%), NaCN	Reag H_2O	105	1.5	1-Cyanooctane	95
1-Bromobutane	214h	NaCN	Ethylene Glycol	101	1	1-Cyanobutane	90
1-Bromobutane	227	NaCN, cat. KI	Cellusolve, H_2O	Reflux	4.6	1-Cyanobutane	69
1-Bromobutane	192	NaCN	DMSO	60-90	0.6	1-Cyanobutane	92

Appendix 11 (Continued)

Reagent	Refs.	Salts	Solvent	Conditions Temp. (°C)	Conditions Time (hr)	Products	Yield (%)
1-Chlorobutane	227	NaCN, cat. KI	Cellusolve,	Reflux	4	1-Cyanobutane	12
1,3-Dibromo-propane	190	NaCN	EtOH, H_2O	100	30-60	1,3-Dicyano-propane	77-86
1,3-Dichloro-propane	191	NaCN	DMSO	160	0.5	1,3-Dicyano-propane	67
1-Bromo-3-chloropropane	190	KCN	EtOH, H_2O	100	1.5	1-Chloro-3-cyanopropane	40-47
1-Bromo-3-chloropropane	222	$C_6H_5\overset{+}{N}(CH_3)_3Cl^-$ (10%), NaCN	CH_2Cl, H_2O	90	1.5	1-Chloro-3-cyanopropane	48
						1,3-Dicyano-propane	23
1-Bromo-3-chloropropane	222	$C_6H_5\overset{+}{N}(CH_3)_3Cl^-$ (10%), NaCN	CH_2Cl, H_2O	90	1.5	1-Chloro-3-cyanopropane	52
				90	6	1,3-Dicyano propane	25
1,4-Dichloro-butane	191	NaCN	DMSO	160	0.5	1,4-Dicyano-butane	88
1,4-Dichloro-butane	191	NaCN	t-BuOH, Ethylene Glycol	100	5	1,4-Dicyano-butane	92
1-Bromobutane	222	$C_6H_5\overset{+}{N}(CH_3)_3Cl^-$ (10%), NaCN	CH_2CH_2, H_2O	90	6	1-Cyanobutane	71.4

Appendix 12. Substitution and Elimination Reactions of Secondary Halides with "Naked" Cyanide.[180]

Substrate	Solv.	Concentration[a] Crown (M)	Concentration[a] Substr. (M)	Temp.	Time $t_{1/2}$[b] (hr)	Time t_{comp}[b] (hr)		Yield glc	Yield nmr[c]	Yield iso.[c]
								(%)		
2-Bromobutane	CH_3Cn	0.14	2.0	Reflux	16	34	2-Cyanobutane	70		37
2-Bromobutane	C_6H_6	0.14	2.0	Reflux	62	66[d] 55[e]	2-Cyanobutane	43		-
2-Bromooctane	CH_3CN	0.12	2.0	Reflux	15	70	2-Cyanooctane	65		56
							Octenes[f]	17		-
2-Chlorooctane	CH_3CN	0.12	2.0	Reflux	59	220[d]	2-Cyanooctane	78		-
							Octenes[f]	3		-
Cyclohexyl Bromide	CH_3CN	0.13	1.8	Reflux	-	54[d]	Cyclohexene[g]	46		-
Cyclohexyl Chloride	CH_3CN	0.15	1.8	Reflux	-	123[d]	Cyclohexene[g]	31		-

[a]The reactions were run in a total of 25 ml of solution, with a 2-fold excess of solid KCN per functional group converted.

[b]The time required for 50% of the starting material to react was defined as $t_{1/2}$, and $t_{completion}$ was the time required for complete formation of the final product.

[c]The half-width band method[228] was used to determine the glc yield, with isolated yields for representative cases. Nmr spectra(where applicable) exhibited only peaks for the stated product.

[d]These reactions were stopped before completion.

[e]Determination of $t_{1/2}$ made by nmr integration using the 18-crown-6 singlet as an internal standard.

[f]Consisted of a mixture of 1-octene and cis-, trans-2-octene by glc comparison with a known mixture.[182]

[g]Identified by overlap of the olefin peak nmr absorption with a known sample.[182]

Appendix 13. Comparison of Literature Methods for Nitrile and Acetate Synthesis.

Run	Substrate	System	Products (Yields)	Reference
1	1-Chlorooctane	Organic Liquid-H_2O, 3 hr, 1% $C_{16}H_{33}PBu_3^+Br^-$, 105	1-Cyanooctane (95.0)	89a
2	1-Chlorooctane	Organic Liquid-H_2O, 1 hr, 5% $C_{16}H_{22}PBr^-$, 90°	1-Cyanooctane (95.0)	89a
3	1-Bromooctane	As above, 1% catalyst, 1.5 hr.	1-Cyanooctane (95.0)	89a
4	1-Bromooctane	KOAC, CH_3CN, 1.44M Substrate, 0.102M crown, 83°, 3 hr.	n-Octylacetate (96.0)	95
5	2-Chlorooctane	KCN, CH_3CN, 0.122M crown, 2.0M Substrate, 83°, 24 hr.	2-Cyanooctane (77.5) Octene (3.1)	96
6	2-Bromooctane	KCN, CH_3CN, 0.16M crown, 2.0M Substrate, 83°, 78 hr.	2-Cyanooctane (56.0) Octenes (17.0)	96
7	2-Bromooctane	Organic Liquid-H_2O, 1.8 hr 1% $C_{16}H_{33}PBu^+Br^-$, 105°	2-Cyanooctane (85-90)	89a
8	2-Chlorooctane	NaCN, DMSO, 1 hr	2-Cyanooctane (70)	191

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162. In other determinations, volumetric flasks with different sizes and reagents with different volumes (i.e., concentrations) were utilized depending upon the relative solubilities of the different salts. For example, since potassium iodide is extremely soluble in acetonitrile (without crown), it was found necessary to minimize the amount of sample used and maximize the size of the volumetric flask so as to get a concentration which would fall in the range of ca. 1.0 x 10^{-3}M and thus would give a relative reading on the scale of the photometer used.

163. (a) It was found necessary to work up the reaction at ambient temperature, especially when evaporating the bulk of the solvent. In Run 7, Table 9, when attempts were made to remove the bulk of the solvent by rotary evaporation with the application of little heat, 2-cyano-2-methylcyclohexanone product 35 along with its isomer, the "Favorskii rearrangement product" 36, were formed with the former predominating. Presumably, in the presence of traces of "naked" cyanide in the flask, the initially formed product 35 would isomerize to the "Favorskii rearrangement product" 36 in varying ratios (ca. 3:1 to 2:1) depending upon the concentration of crown, "naked" cyanide, and the time of heating; (b) K. C. Auwers, T. Bahr, and E. Frese, Ann., 441, 68 (1925); (c) R. E. Meyer, Helv. Chim. Acta., 16, 1291 (1933); (d) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, J. Amer. Chem. Soc., 69, 2942 (1947); (e) W. R. Schleigh and F. D. Popp, J. Chem. Soc., 760 (1966).

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